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THE SIGNIFICANCE AND TREATMENT OF POLYPS OF THE COLON AND RECTUM*

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IN a review of records of patients studied at the Lahey Clinic twenty or more years ago, it is not unusual to see a diagnosis noted "polyp of rectum or colon; patient to have periodic checkups." Since that time the true significance of rectal and colon polyps has been quite generally appreciated, and at present not only are increasing numbers of patients of all ages and both sexes being found to have polyps but also these polyps are being removed or destroyed without delay.

On the basis of current knowledge of this subject, the association of polyps with cancer of the rectum and colon is generally accepted.[1-9] Several points concerning the incidence and characteristics of polyps are worth emphasizing:

In the first place, benign mucosal polyps of the rectum and colon occur in both sexes, slightly more often in males than in females, and at all ages; they are more frequent in the older age groups.

Secondly, they are often multiple and, in our experience, occur in 25 per cent of all surgical specimens removed for cancer of these organs (Fig. 1).

Thirdly, there is a definite similarity between the location of benign mucosal polyps and carcinoma of the rectum and colon (Table 1).

Fourthly, all stages between benign mucosal polyps and carcinoma of the colon and rectum can be demonstrated histologically.

Fifthly, benign mucosal polyps are true tumors because of some inherent defect in their cellular growth, and are not the result of an inflammatory process. They must be considered as premalignant lesions.

And, finally, a high percentage of the malignant lesions of the colon and rectum originate in a pre-existing benign mucosal polyp. Therefore, when such premalignant lesions are discovered they should be removed or destroyed without delay.

Neoplastic disease of the colon and rectum is thus characterized by many factors that make it more favorable for cure than many other types of cancer, such as that of the stomach or of the lung. Cancer of the colon and rectum tends to develop relatively slowly, frequently metastasizes late and commonly causes symptoms early in its development. Of greater significance is the fact that a high percentage of these tumors originate in a pre-existing benign lesion, which in most cases can be removed or destroyed with relative ease. It is imperative, therefore, that all physicians, whether they are interested in general medicine or in surgery, be aware of the frequency and significance of benign mucosal polyps of the rectum and colon.

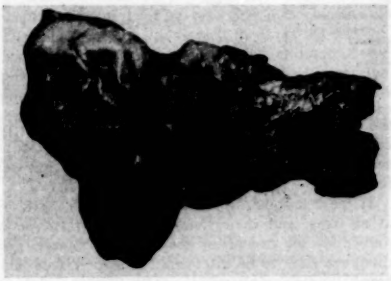

FIGURE 1. *Resected Specimen of Rectum, Showing Adenocarcinoma with Associated Multiple Benign Mucosal Polyps.*

At the Lahey Clinic we have had an extensive experience with this subject and have recently completed a statistical survey of 400 patients treated between 1945 and 1950. It is the purpose of this paper to review many of the problems encountered and to present some of the lessons learned concerning the discovery and removal or destruction of these premalignant tumors.

Polyps of the rectum and colon occur much more frequently than has generally been recognized. In

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a study[7] based on the 1843 consecutive autopsies performed at the Pathological Laboratory of the New England Deaconess Hospital on patients dying of all causes between 1935 and 1945 the incidence of benign polyps of the colon and rectum was 7 per cent. Helwig[4] has reported an incidence of 9.5 per cent in an autopsy series of 1460 patients. At the clinic, polyps are being discovered in 5 per cent of patients over thirty-five years of age being sigmoidoscoped regardless of symptoms. In the autopsy study, polyps were found to be single in 58 per cent and multiple in 42 per cent of cases. Clinically, single polyps were observed in 73 per cent of the patients examined and multiple polyps in 27 per cent. The clinical studies also revealed that 56 per cent of the patients were males and 44 per cent were females.

TABLE 1. *Incidence by Location of Benign Polyps and Malignant Tumors of the Colon (1935 to 1945, Autopsy Series).*

Location	Cancer		Benign Polyps	
	No. of cases	Percentage	No. of cases	Percentage
Cecum Ascending colon	27	13.0	64	20.5
Hepatic flexure Transverse colon Splenic flexure	28	13.5	85	27.3
Descending colon Sigmoid Rectum Anus	152	73.5	162	52.2
Totals	207		311	

If these lesions are so common in both sexes and at all ages, and their removal so important in the prevention of cancer of the terminal bowel, how, then, are they to be discovered in appreciable numbers? Large numbers of polyps will not be discovered if examinations of this region are confined to patients with the classic symptoms of rectal bleeding, alterations in bowel function or unexplained abdominal pain. It is the policy at the clinic to include a sigmoidoscopic examination on all patients who report for a complete physical examination. It is difficult to determine accurately the percentage of benign polyps that cause symptoms because of the frequent association of anorectal disease, but it is estimated that less than a third of patients with polyps have associated rectal bleeding or other bowel symptoms. It is only by the inclusion of routine sigmoidoscopic examinations as a part of every complete examination that the majority of such polyps will be discovered at a time when they can easily be managed and cancer in this region prevented. The increase in the number of benign polyps detected in our patients has been in direct proportion to the number of sigmoidoscopic examinations performed regardless of symptomatology.

Digital examination of the rectum is carefully performed on all patients who report to the clinic for complete physical examinations. Certain patients should be sigmoidoscoped without preparation. These patients may have had diarrhea recently, an active colitis, some other intra-abdominal inflammatory condition, obvious bowel obstruction or an easily palpable rectal tumor. When organic disease of the terminal bowel is to be ruled out and there are no contraindications, patients are carefully prepared before instrumental and radiographic studies are made.

Castor oil, 45 to 60 cc., is taken by the patient the night before the examination. On the morning of the examination a colonic irrigation is given at the clinic under trained supervision. The sigmoidoscopic examination may be done a short time after this irrigation. If this routine is followed, adequate suction equipment must be available. Two or three hours after the sigmoidoscopic examination radiographic studies of the colon can be made satisfactorily. This interval is necessary to permit the air that entered the colon at the time of instrumental examination to be evacuated so that it will not interfere with subsequent radiographic studies.

FIGURE 2. *Demonstration of a Benign Mucosal Polyp of the Sigmoid with a Barium-Enema Examination.*

The technic of radiographic study of the terminal bowel has previously been reported[8] in detail. We have never been completely satisfied with the number of polyps that have been discovered by radiographic means in the portion of the bowel above the reach of the 25-cm. sigmoidoscope (Fig. 2). The bowel must be completely empty, and the examination must be performed by an experienced radiologist. It has been our custom to perform a routine barium-enema study at the first examination. Addi-

tional contrast air studies of the colon are not carried out as a routine procedure but are performed as a separate examination and after a separate preparation of the colon if the usual barium-enema studies are not satisfactory or organic disease is still suspected after these studies have been reported as negative. Polyps overlooked with the usual barium-enema technic have been found as a result of contrast air studies.

A common error in our experience that still occurs all too frequently in practice is the dependence upon roentgenologic studies of the colon for the detection of polyps of the rectum and colon or other organic disease (Table 2). Of 150 patients, 15 were found to have benign lesions in the rectum and rectosigmoid by sigmoidoscopic examination; with the known presence of the tumors radiologically it was possible to confirm these findings in only 5 patients. Radiologists and clinicians both would do well to insist that when organic disease of the colon or rectum is suspected, a careful sigmoidoscopic examination of the terminal bowel be made before radiographic studies of the colon are performed.

TABLE 2. *Results of Radiographic Studies of the Colon and Rectum (Barium-Enema and Contrast Air Technics).*

RESULT OF EXAMINATION	NO. OF CASES	PERCENTAGE
Patients with bleeding (23 with hemorrhoids or fissure)	62	41
Investigation of other symptoms	88	59
Polyps visualized with sigmoidoscope	15	
Polyps visualized on x-ray film	5	
Total patients with polyps	16	

In our clinical experience over 80 per cent of all benign polyps have been within reach of the 25-cm. sigmoidoscope. In the autopsy series 52 per cent were found in this area (Table 1).

To increase further the discovery of benign mucosal polyps in the rectum and colon there must be general acceptance of the idea that the sigmoidoscope as an examining instrument should be as familiar to the physician as the stethoscope, the vaginal speculum or the ophthalmoscope. Surgeons have been aware of the significance of sigmoidoscopic examinations, but internists and all physicians doing general diagnostic work also should fully appreciate the value of this instrument.

In this discussion the term polyp is defined as a tumor arising from the mucous membrane of the colon or rectum. Hypertrophied anal papillae, hemorrhoids and other tumors arising in the anal canal are not included. Polyps may be sessile or pedunculated. The majority are adenomatous and should properly be referred to as adenomas. Our pathologists report all benign tumors of this type as mucosal polyps without further differentiation. From a clinical standpoint, however, particular attention must be given to papillary adenomas or the villous type[10] of tumor because of their differences in clinical behavior from the usual adenoma. Eight per cent of polyps in our series were of the papillary variety. Sunderland and Binkley,[11] from the Memorial Hospital, have carefully reviewed this subject, and there is little that we can add to their discussion. Our experience closely parallels theirs. The basic difference between papillomas and adenomas is in their manner of growth. The adenoma is a tumor of mucosal glands, with little if any involvement of the surface epithelium. The papilloma is a tumor primarily of the mucosal surface epithelium, with resulting secondary glandular changes and a tendency for growth by lateral spread. In our experience, although the adenoma rarely recurs after fulguration or excision, recurrences after local treatment of the papilloma are almost inevitable unless some type of resection is performed.

The detection of invasive cancer in either the adenomas or the papillomas is well understood by surgeons and pathologists who have had extensive experience with this disease. However, patients are frequently referred to the Lahey Clinic with a diagnosis of low-grade cancer of the colon or rectum that is based on the histologic study of a biopsy specimen and with which we cannot agree as a result of our own histologic and clinical investigations.

Tumors within reach of the examining finger or easily palpated by the examining instrument that present induration, fixation, firmness and ulceration must always be considered to be malignant. Warren and Swinton,[8] in 1939, presented the histologic criteria of malignancy in tumors of this type that are believed to have withstood the test of time:

> If we accept three important criteria of malignancy — anaplasia, irregularity of architecture and invasion — it is necessary to have at least two of these three factors present before making a diagnosis of malignant disease. It is possible for any of these three criteria to be present without actual malignancy with one exception, definite lymphatic or intravascular invasion means cancer.

Meissner,[9] Warren's associate, in a more recent publication, has enumerated certain other criteria:

> Cancer must not be diagnosed on the mere presence of numerous mitoses in the tumor. Benign polyps often show many mitoses. Epithelial cells often occur within vessels as artefacts produced by cutting the tissue. The diagnosis of cancer of the intravascular epithelial cells should at least be associated with a thrombus and preferably be actually invading the vessel wall. All portions of the biopsy specimen must be examined before a negative report is made, otherwise a small focus of malignant change may be overlooked. The diagnosis of cancer should never be made on borderline evidence. A pathologist should not feel compelled to diagnose tissue which is inadequate. Both the clinician and the pathologist must appreciate that repeated biopsies may be necessary before a definite decision can be made.

It is needless to add that in the study of any tissue of this type a review must be made of the entire tumor, together with its base, before neoplastic disease can be excluded.

The majority of the polyps found in our 400 patients were small lesions that were destroyed immediately by fulguration, biopsies not being taken in many cases. Of these polyps 230 were destroyed by fulguration, 44 were removed by snare excision and fulguration, 34 by surgical excision, and 30 by colotomy; 69 required some type of resection, and 4 patients refused treatment.

The pathological findings were as follows: benign mucosal polyps, 218 cases; benign mucosal polyps with early carcinoma, 38 cases; and no pathological change, 151 cases. Benign mucosal polyps were associated with carcinoma of the rectum in 50 patients, with carcinoma of the colon in 19 and with chronic ulcerative colitis in 10.

It has been our policy to fulgurate with the high-frequency unit without biopsy all small, adenomatous polyps that are easily reached with the sigmoidoscope and are below the peritoneal reflection and obviously benign. To date we have had no reason to regret this program.

We have removed with the high-frequency electric snare polyps with a definite pedicle that can be reached easily even though, in certain cases, they may be above the peritoneal reflection but in which the base of the pedicle can be approached without difficulty and can be observed clearly. Polyps at a high level that cannot easily be reached or in which the entire pedicle cannot be clearly observed are removed by colotomy. Obviously, tumors detected by radiographic study of the colon have also been removed by colotomy. We have had no experience with the treatment of tumors of this type by the local application of radium or high-voltage therapy.

FIGURE 3. *Blood-Vessel Invasion in Early Adenocarcinoma Arising in a Benign Mucosal Polyp.*

The principal problem in the treatment of these tumors has been with the management of the papillary adenoma because of their tendency to recur locally; over half the patients who have not had some type of resection have had repeated recurrences. In 3 patients, during the period of repeated fulgurations, invasive carcinoma ultimately developed, requiring radical resection. It has been impossible to predict which tumors will tend to become malignant and which will tend to recur locally. Sunderland and Binkley[11] have stated that in their experience no tumor that showed a uniformly benign structure originally and in the early recurrences had developed into carcinoma to date. Our tendency at present, however, is to employ some type of resection in the treatment of these papillary lesions.

Buie[2] has reviewed in detail his vast experience with the fulguration of rectal tumors. We do not disagree with his policy except that in our opinion, when all facilities for any type of treatment are available, most tumors that can be clearly seen and are within reach of the 25-cm. instrument can be treated locally. In our entire experience only 2 cases of perforation have followed fulguration. In 1 of these too much tissue was probably destroyed at one sitting. The second perforation occurred in the fulguration of a small, obviously malignant lesion. This fulguration had been done to control bleeding from biopsy. In both cases immediate resection was performed satisfactorily. On only one occasion has it been necessary to resort to resection for hemorrhage after biopsy and fulguration. However, the danger of hemorrhage must be thoroughly appreciated. The blood supply to these tumors is frequently vigorous, and if biopsies are taken in tumors lying above the peritoneal reflection hemorrhage may be very troublesome, requiring the utmost in experience, skill and equipment.

Treatment of polyps with localized areas of invasive cancer presents a serious problem.[12-14] If it can be satisfactorily demonstrated that there is no malignant degeneration of the pedicle or base of the tumor and no evidence of blood-vessel or lymphatic invasion by the cancer (Fig. 3), complete local excision of the tumor is sufficient. Isolated cases of lymph-node involvement in polyps of this type have been reported in the literature, but to date this has not occurred in our experience. It is true that in certain cases segmental resection of the bowel may be necessary for complete histologic examination of the polypoid tissue, but we do not believe that segmental resection is necessary for all polyps of the colon. If invasive cancer is found and there is any suggestion that it may have spread beyond the pedicle of the polyp, radical resection should be done. Polyps, particularly those in the descending colon, usually have a long pedicle of normal mucosa. Such polyps can easily be removed completely by simple colotomy and without bowel resection.

The treatment of the congenital type of multiple polyposis of the colon and rectum presents a special problem.[15] This subject is, in general, well understood. In the past all these patients died of cancer. The oldest reported patient in our experience died at the age of forty-nine years of multiple cancers of the colon. At this clinic the treatment has usually consisted of resection of the colon and anastomosis of the ileum to the upper rectum or lower sigmoid, with fulguration of all polypoid tissue in the rectum, usually before the resection. Over the years, however, cancer developed in the rectal segment in 2 of these patients. Because of this experience and because others have had a similar experience, we believe that unless the patient's course can be followed very closely, the most desirable treatment is removal of the entire bowel.

The relation of polypoid disease to chronic ulcerative colitis is an important problem.[16-18] In the past we did not believe that pseudopolyposis of the colon resulting from the inflammatory process in chronic ulcerative colitis had any significant relation to neoplastic disease. However, it has become increasingly apparent that cancer of the colon and rectum develops much more commonly in patients who have had chronic ulcerative colitis than in those who have not. Counsell and Dukes[18] reported carcinoma of the colon in 11 per cent of surgically removed specimens of chronic ulcerative colitis. More important, they point out that half the patients who had had the disease for ten years or more were found to have cancer at the time of their surgical treatment. Cattell[16, 17] has also reported from this clinic that 1 in 3 patients who had ulcerative colitis for over nine years had associated lesions. It must further be appreciated that the carcinoma developing in chronic ulcerative colitis usually grows rapidly, metastasizes early and is of a high degree of malignancy.

We have attempted during this past year to follow the 400 patients mentioned in this study. It has not been possible to complete this investigation, but from the figures obtained to date, certain suggestive data are emphasized.

Of patients examined sigmoidoscopically and roentgenographically, 136 followed for more than five years were found not to have further polyps or carcinoma. The group of 150 patients followed between one and five years also were free of colonic and rectal disease. Fourteen of the patients died of causes that, so far as we could determine, were not related to disease of the colon or rectum. It has not been possible to obtain complete follow-up studies on 74 patients in this series. However, subsequent polyps have been found in 16 and subsequent cancer in 10 of this group.

The incidence of further pathologic change in more than 6 per cent of the entire series, or in more than 8 per cent of patients followed to date, makes it imperative that patients with polyps as well as those who have had carcinoma of the colon and rectum be followed periodically indefinitely. We believe that this incidence of the subsequent development of polypoid lesions of the colon and rectum will further increase in this series as time elapses.

One of the questions that we have faced at the clinic has been, How often should these patients be examined? We have a number of patients who come to us annually for complete physical examinations. On the basis of our experience to date we do not believe that it is necessary to include a sigmoidoscopic examination every year in the absence of any rectal and colonic symptoms or previous colonic disease. It is probably satisfactory to perform sigmoidoscopic examinations at two-year intervals provided there is no recent history of rectal or colonic difficulty. When we have fulgurated a polyp without a biopsy it is our policy to repeat these examinations at the end of six weeks to determine whether the tumor is entirely destroyed, and also at three months and again at six months to be certain that there is no tendency to recurrence or the subsequent development of polypoid disease. After the first year, annual examinations are done. Although we have seen cancer of the colon and rectum that developed without passing through an intermediary polypoid stage, in our experience, polyps have been of relatively slow growth.

Conclusions

Polyps of the colon and rectum occur frequently and are true tumors and forerunners of one of the most common forms of cancer. If increasing numbers of patients are properly examined for this condition at regular intervals and when these premalignant tumors are discovered if they are either removed or destroyed, the ideal approach to the problem of cancer of the terminal bowel will gradually be achieved — that is, prevention.

References

1. Bacon, H. E., and Broad, G. G. Pathogenesis of adenomatous polyps in relation to malignancy of large bowel. *Rev. Gastroenterol.* 15: 284-295, 1948.
2. Buie, L. A. Polypoid disease of colon. *Postgrad. Med.* 5:177-183, 1949.
3. Cattell, R. B. Surgical treatment of polyps of large intestine. *Am. J. Surg.* 76:733-747, 1948.
4. Helwig, E. B. Evolution of adenomas of large intestine and their relation to carcinoma. *Surg., Gynec. & Obst.* 84:36-49, 1947.
5. Jackman, R. J., and Mayo, C. W. Adenoma-carcinoma sequence in cancer of colon. *Surg., Gynec. & Obst.* 93:327-330, 1951.
6. Swinton, N. W., and Doane, W. A. Polyps of colon and rectum. *S. Clin. North America* 32:923-935, 1952.
7. Swinton, N. W., and Haug, A. D. Frequency of precancerous lesions in rectum and colon. *Lahey Clin. Bull.* 6:84-88, 1947.
8. Swinton, N. W., and Warren, S. Polyps of colon and rectum and their relation to malignancy. *J. A. M. A.* 113:1927-1933, 1939.
9. Swinton, N. W., Hare, H. F., and Meissner, W. A. Diagnosis of cancer of large bowel. *J.A.M.A.* 140:463-469, 1949.
10. Ewing, M. R. Villous tumours of rectum. *Ann. Roy. Coll. Surgeons England* 6:413-441, 1950.
11. Sunderland, D. A., and Binkley, G. E. Papillary adenomas of large intestine; clinical and morphological study of 48 cases. *Cancer* 1:184-207, 1948.
12. Lockhart-Mummery, H. E., and Dukes, C. E. Surgical treatment of malignant rectal polyps. *Lancet* 2:751-755, 1952.

13. McLanahan, S., Grove, G. P., and Kieffer, R. F., Jr. Conservative surgical management for certain rectal adenomas showing malignant change. *J. A. M. A.* 141:822-826, 1949.
14. Swinton, N. W. Diagnosis and treatment of mucosal polyps of rectum and colon, with early malignant change. *Am. J. Surg.* 75:369-373, 1948.
15. Dukes, C. E. Familial intestinal polyposis. *Ann. Roy. Coll. Surgeons England* 10:293-304, 1952.
16. Cattell, R. B. Surgical treatment of ulcerative colitis. *Gastroenterology* 10:63-66, 1948.
17. Cattell, R. B., and Boehme, E. J. Importance of malignant degeneration as complication of chronic ulcerative colitis. *Gastroenterology* 8:695-710, 1947.
18. Counsell, P. B., and Dukes, C. E. Association of chronic ulcerative colitis and carcinoma of rectum and colon. *Brit. J. Surg.* 39:485-495, 1952.

THE WORK WEEK OF PHYSICIANS IN PRIVATE PRACTICE

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RECOGNITION that the health of the people is fundamental to the full achievement of national potentials, that the key role in health is played by the physician and that the volume of services rendered by physicians must be sufficient to meet these responsibilities has prompted a variety of professional organizations, governmental agencies and other interested groups to develop considerable data concerning the sociologic and economic aspects of the medical profession. The American Medical Association, for example, has reported on the size of the physician population, its composition by age groups, its make-up by field of specialization and type of practice and the pregraduate and postgraduate opportunities for training. Other groups have undertaken spot surveys from time to time. These surveys have examined educational facilities and hospital training programs for physicians, appraised the effects of the military mobilization of physicians on civilian health services and investigated other aspects of medical service.

In 1950 the Department of Commerce and the American Medical Association jointly surveyed physicians in the United States. The data collected included information concerning income levels, specialty, age, geographic location and length of work week. These data have been made available to the Health Resources Advisory Committee for use in studies of military and civilian demands on the national health resources.

Participating in the survey were more than 55,000 physicians.§ A report has already been published concerning income levels.[1] The present report deals primarily with hourly work weeks.

Active and Inactive Physicians

About 93 per cent of the 55,000 physicians participating in the survey reported they were actively engaged in the practice of medicine. Some of these physicians, especially those in the older age groups, worked relatively few hours each week, but all devoted a minimum of several hours a week to their profession. Fully retired and no longer in practice were the remaining 7 per cent — a proportion somewhat larger than the 5 per cent reported as retired by the *Directory of the American Medical Association* in 1950 (Table 1).

Table 1. *Fully Retired Physicians by Age Groups, United States, 1949.*

Age Group	No. of Physicians Responding	No. Fully Retired
Under 35	6,568	24 (0.4%)
35–44	14,037	55 (0.4%)
45–54	9,120	177 (1.9%)
55–64	6,137	587 (9.6%)
Over 64	7,812	2,806 (35.9%)
Unknown	11,559	357 (3.1%)
Totals	55,233	4,006 (7.3%)

According to this study, no appreciable proportion of physicians enter full retirement until the age of sixty-five — less than 1 per cent of the physicians under fifty-five years of age being retired, about 10 per cent of those from fifty-five to sixty-four years of age, but more than a third of those over sixty-four.

Physicians in Private Practice

Of the 55,000 physicians participating in the study, more than 30,000 reported that they were in private practice. The remainder of this paper deals with these physicians. Their work weeks encompassed a wide range of hours, extending from less than ten to more than ninety. More than half of them worked sixty hours or more a week — a total work week 50 per cent greater than the accepted norm of forty hours a week (Fig. 1).

Age is a factor that greatly influences the work week of physicians in private practice. The average

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§In the first mailing of the survey, questionnaires were sent to approximately 100,000 of the 201,277 physicians (inactive as well as active, and to interns, residents, fellows and so forth) listed in the alphabetical IBM card file maintained by the Bureau of Medical Economic Research of the American Medical Association. The 100,000 physicians represented every other name in the file. Usable returns from this mailing numbered 39,295 — roughly 20 per cent of the physicians in the United States in 1949. Approximately 10,000 buff and 15,000 green questionnaires were sent out in subsequent mailings. The buffs represented every tenth physician not selected for the first mailing, and the greens every sixth physician not hitherto sampled. These mailings provided 11,932 additional returns for study. Thus, the entire usable sample totaled 51,227, or 25 per cent of the physicians in the United States. In addition, returns were received for 4,006 physicians who stated that they were fully retired, making a total of 55,233 returns. The Department of Commerce in its report on the incomes of physicians used the data for only 29,878, or roughly half these physicians, as its sample. The Health Resources Advisory Committee has used the questionnaires for the entire 55,233 physicians in this study of physician employment patterns. Comparisons of such characteristics as geographic location, age distribution and degree of specialization between all physicians in the United States and those for whom returns were received showed the sample used in this study as representative of the total physician population.

work week for those sixty-five years of age and older was less than half that of younger physicians in the group thirty-five to forty-four years of age.

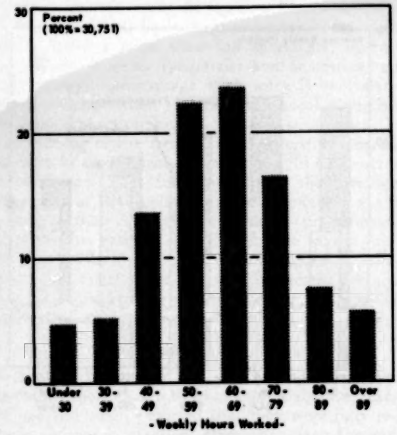

FIGURE 1. *Average Hours.*

Similarly, those fifty-five to sixty-four years old had an average work week roughly three fourths as long as those of thirty-five to forty-four. This

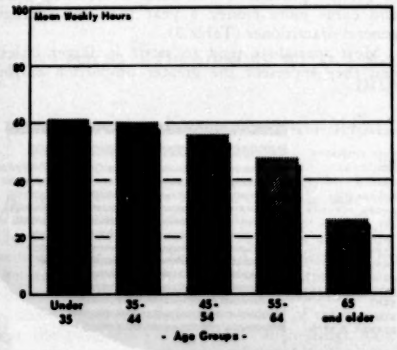

FIGURE 2. *Hours Worked Each Week, According to Age of Physicians in Private Practice.*

relation was observed for both general practitioners and full-time specialists (Fig. 2).

PHYSICIAN-POPULATION RATIO

Besides the age factor, the supply of physicians in different localities also strongly influences the length of work week for those in private practice. During 1949 there was about 1 physician in private practice for every 1000 of civilian population for the country as a whole. This ratio varied sharply, however, among the individual states. Nine states had less than 70 physicians in private practice per 100,000 civilian population; another 17 had between 70 and 89; and the remaining 23, including the District of Columbia, had 90 or more. On an over-all basis, the length of the work week was closely related to the physician-population ratio (Table 2).

TABLE 2. *Work Week of Physicians in Private Practice by States According to Physician-Population Ratios, 1949.*

Physicians per 100,000 Population	No. of States	Work Week		
		Total	General Practitioners	Full Specialists
		hr.	hr.	hr.
50-59	4	62.6	65.0	58.1
60-69	5	61.5	63.1	59.3
70-79	8	60.6	62.3	58.2
80-89	9	60.0	62.0	57.0
90-99	9	59.7	62.2	55.8
100 and over	14	54.8	55.2	53.7

More than half the physicians in the United States in 1949 resided in the better-staffed states — those where the physician-population ratio was 100 per 100,000 or more. These men worked an average of fifty-four and eight-tenths hours per week, and their net annual income was $10,600; the remaining half — those in the poorer-staffed states — worked an average of sixty and a half hours a week and reported an average net annual income of $12,000. Thus, the work week for physicians in better-staffed states is 9 per cent shorter, and their net annual income is 12 per cent less. This disparity indicates that the hourly rate of payment as well as the total income of physicians located in better-staffed states is lower. This lower average income is surprising since the average per capita income of the general population in these states is relatively high; California, Colorado, Connecticut, Delaware, District of Columbia, Illinois, Massachusetts, Nevada, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island and Vermont.

TABLE 3. *Average Earnings of Specialists and General Practitioners.*

Type of Practice	Average Work Week	Net Annual Income
	hr.	$
General	60.6	9,300
Full specialty	55.4	14,000

EFFECT OF SPECIALIZATION

The trend toward specialization, one of the most characteristic features of the United States, is most generally associated with the industrial economy.

But specialization has also come to play an increasingly important role in the practice of medical science. According to information made available by the American Medical Association, the proportion of specialists among physicians has more than tripled over the past thirty years: 10 per cent of the physicians in 1923 but more than 30 per cent in 1949 were restricting their practice to some specialized field of medicine. Furthermore, the upward trend is continuing. A survey of 1940 graduates conducted by Weisskotten and Altenderfer[2] in 1950

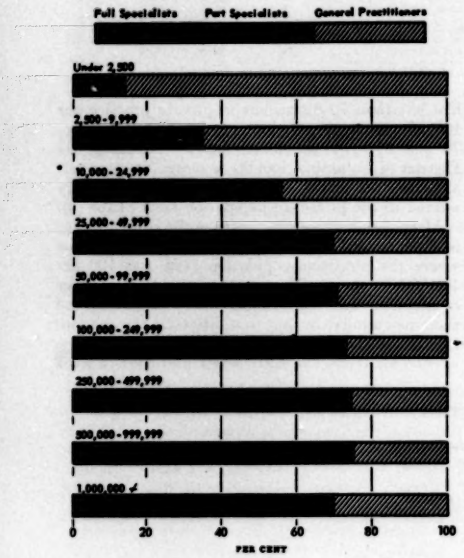

FIGURE 3. *Physician Staffing Patterns According to Degrees of Specialization and Size of Community (1949).*

showed that two thirds of them were restricting their practice to a specialty. Not all today's full-time specialists have taken residency training, but the proportion taking such training is increasing sharply. More than half the first-year interns in 1949, 1950 and 1951 continued their training in residencies or fellowships without interruption after internship, according to surveys of the Health Resources Advisory Committee. Additional numbers of physicians resume hospital training after an interruption of a year or more.

Whether or not a physician specializes has a great deal to do with his income, the number of hours he works and where he lives, according to the information collected by the Department of Commerce and the American Medical Association. These data showed that the typical full specialist

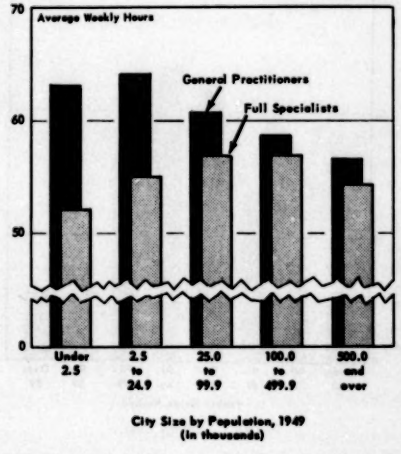

FIGURE 4. *Effect of Type of Practice and Size of Community on Length of Work Week.*

in private practice works fewer hours each week and earns more money a year than the average general practitioner (Table 3).

Most specialists tend to settle in larger cities, and they represent the greater proportion of the

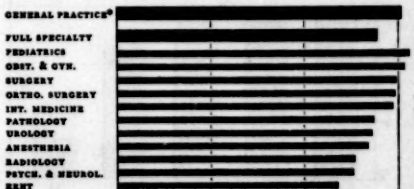

FIGURE 5. *Average Number of Hours Worked Each Week by Physicians in Private Practice.*

total physicians in private practice in urban areas (Fig. 3).

Full specialists in cities of 25,000 to 500,000 have longer work weeks than those in smaller or in larger

communities. For general practitioners, on the other hand, the hourly work week is longest in rural communities, shortening as the size of the city grows larger (Fig. 4). Income shows similar variations, as pointed out in the report of Weinfeld.[1]

On an over-all basis, general practitioners work more hours a week than full specialists; in two specialties, however (pediatrics and obstetrics and gynecology), the average work week is over sixty hours — longer than that for the typical physician in general practice (Fig. 5).

Evidence of the trend toward specialization can be seen in a comparison of average ages for general practitioners and full specialists, the average specialist in 1949 being two and four-tenths years younger than the typical general practitioner. Among the various specialties, there was a difference in average age of as much as eight and eight-tenths years; the specialty with the lowest average age was anesthesia — a relatively new and rapidly expanding medical specialty (Table 4).

Summary

About 7 per cent of all participating physicians, including more than a third of those sixty-five years of age and older, reported that they were fully retired and not in practice. Physicians sixty-five and older who were in practice reported a work week less than half as long as the average for physicians under forty-five years of age. More than half the physicians in private practice worked sixty hours or more a week, according to a study of the information reported by more than 30,000 physicians in 1949.

The length of work week for physicians is closely related to physician-population ratios — men in better-staffed states work fewer hours a week. Specialists work fewer hours and earn more money than general practitioners, on the average.

Most specialists are located in larger cities, and they represent a considerably greater proportion of the total physician staffing in urban areas. The typical specialist in 1949 was more than two years younger than the average general practitioner.

Table 4. *Median Age of Physicians in Private Practice by Field of Practice (1949).*

Field of Practice	Median Age
	yr.
General Practitioners*	45.7
Full Specialists	43.3
Eye, ear, nose and throat	48.1
Dermatology and syphilology	45.0
Urology	43.8
Allergy	43.4
Radiology	43.2
Surgery	43.2
Neurology and psychiatry	43.1
Obstetrics and gynecology	42.9
Pathology	42.7
Internal medicine	42.1
Pediatrics	41.9
Orthopedic surgery	41.6
Anesthesia	39.3

*Includes part-time specialists.

References

1. Weinfeld, W. Income of physicians, 1929-49. *Survey of Current Business* 31:9-26, 1951.
2. Weiskotten, H. G., and Altenderfer, M. E. Trends in medical practice: analysis of distribution and characteristics of medical college graduates, 1914-40. *J. M. Educ.* 27:3-41, 1952.

CLINICAL EXPERIENCES WITH A NEW ORALLY ADMINISTERED MERCURIAL DIURETIC*

Elliott Bresnick, M.D.,† and Julius Abramson, M.D.‡

BOSTON

A REVIEW of the literature reveals that the use of orally administered diuretic drugs in the therapy of congestive heart failure is gaining wide acceptance.[1-5] The ease of administration by the oral route, obviating visits to an outpatient department and thus lessening the burden on the patient, makes it a desirable method of treatment. For the past few years, several such drugs have been given to ambulatory patients in the outpatient clinic at the Boston City Hospital. This article presents the results obtained with an oral diuretic preparation now known as Neohydrin (3-chloromercuri-2-methoxy-propylurea).§

Fifteen patients with severe congestive heart failure were studied. Before Neohydrin was administered they had been on other therapy for periods varying from four to eighty-one months, with an average of forty-five months. They were given Neohydrin for periods of six weeks to eighteen months, with an average of approximately seven and a half months. Most patients were started on 3 tablets every morning as a trial, and this dosage was gradually increased until the effective level was reached. With one exception, the diuretic was given for six days of each week. Experience has shown that a daily undivided dose is more effi-

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§Kindly supplied by Lakeside Laboratories, Incorporated, Milwaukee, Wisconsin. (Each tablet represents 10 mg. of mercury.)

cacious than the same amount of medication divided into 2 or 3 doses. Therefore, in this study, all the Neohydrin tablets were taken shortly after breakfast. All patients were given digitalis, ammonium chloride and (except when noted) low-salt diets. The efficacy of therapy was evaluated on the basis of subjective criteria such as breathlessness, paroxysmal nocturnal dyspnea and cough, but more especially on the basis of objective criteria such as hyperpnea, pulmonary rales, palpable liver, ascites, edema and body weight.

Nine patients had been on another oral mercurial diuretic, Salyrgan-theophylline Oral* (hereinafter referred to as STO). Experiences with several of these patients were reported previously.[8]

Seven patients were male, and 8 were female. The ages ranged from thirty-four to seventy-two

TABLE 1. *Clinical Results in 15 Patients Treated with Neohydrin.*

Case No.	Control Period	Duration of Treatment with Neohydrin mo.	Dose* tablets/day	Result	Toxicity
1	Digitalis for 60 mo.; parenteral mercurial diuretics once weekly for 10 mo., followed by STO, 7 tablets 6 days weekly for 50 mo., with good results; no toxicity with STO.	17	7	Good — constant normal compensation maintained	On rare occasions, slight nausea and gingivitis; however, throughout entire period Neohydrin never omitted.
2	Digitalis for 51 mo. and 8 tablets of STO daily 6 days weekly for this period; good results; gastrointestinal bleeding and gingivitis once.	18	5	Good — normal compensation maintained; patient frequently increased salt intake, without reappearance of failure.	None; routine x-ray films of upper and lower intestine normal.
3	Digitalis and STO for 34 mo.; in this period STO dose varied between 4 and 6 tablets 6 days weekly; Thiomerin injection occasionally required to maintain adequate compensation; no toxic symptoms.	1½	5	When patient adhered to salt restrictions she maintained adequate compensation, but because she was unpredictable in this respect, requiring parenteral injections whenever she took excessive amounts of salt, it was decided to discontinue further study	None
4	Digitalis for 32 mo.; STO, 6 tablets 6 days weekly, for 32 mo.; 2 cc. of Thiomerin also required once weekly; this combination resulted in less than adequate compensation; increasing dose of STO produced nausea and vomiting.	2½	6	Adequate compensation maintained with this dose, but because of frequent recurrence of toxic symptoms Neohydrin omitted; subsequently, Thiomerin, 2 cc. 3 times weekly, required to maintain adequate compensation.	Abdominal cramps during 1st wk. of treatment; during 2d wk. gross red blood seen in stool once; sigmoidoscopy negative except for "hemorrhoids"; no recurrence of bleeding but frequent nausea and vomiting.
5	Duration of 52 mo.; digitalis and parenterally administered mercurial diuretics once weekly for 24 mo., followed by STO, 8 tablets daily for 6 days weekly for 28 mo.; good compensation, but Thiomerin required periodically; no toxic symptoms.	4	6	Good — adequate compensation; at end of 4 mo. nodular liver felt; patient admitted to hospital and died 1 mo. later (diagnosis, cancer of stomach).	None
6	Duration of 15½ mo.; digitalis and Thiomerin given in 2-cc. doses once weekly for 3 mo., followed by cation-exchange resins for 9 mo. and finally STO, 6 tablets 6 days weekly for 3½ mo.; good results except for persistence of +/+ edema of ankles; no toxic symptoms.	12	3	This patient took all his tablets at night, obtaining excellent diuresis on the following day and maintaining adequate compensation except for + edema of ankles	None
7	Digitalis for 6 mo.; STO, 5 tablets 6 days weekly started but omitted after 1 mo. because of nausea and vomiting; cation-exchange resins given but omitted after a few days because they were poorly tolerated; parenteral mercurial injections given 3 times weekly; in spite of this therapy pleural effusion developed.	5½	3	Patient started on 5 tablets 6 days weekly; dose completely eliminated pleural effusion; dose cut to 3 tablets 5 days weekly and maintained adequate compensation for 1 mo.; increasing signs of failure then developed; dose increased to 5 tablets 6 days weekly, with adequate compensation during last 4½ mo.; patient given only 2 injections of Thiomerin (2 cc. each), requiring none later; at end of 5½ mo. severe failure developed; patient admitted to hospital and died 1 mo. later.	None
8	Duration of 8 mo.; cation-exchange resins and ammonium chloride not tolerated; Thiomerin, 2 cc., given 3 times weekly, with less than adequate compensation.	15	3	Patient given 5 tablets for first 6 wk., with 1 Thiomerin injection (omitted for 10 days because of toxic effects); resumed 5 tablets with poor results; digitalis increased to 0.1 and 0.2 gm. on alternate days; good results since then, with Neohydrin cut to 3 tablets.	Nausea, vomiting and abdominal cramps; blood in stools once; sigmoidoscopy showed no ulceration but friable dilated arterioles, which oozed if traumatized; no recurrence of symptoms.

*For 6 days weekly.

[8] Available from Winthrop-Stearns, Incorporated, New York City. (Each tablet represents 31.7 mg. of mercury.)

years, with an average age of fifty-four years. One patient (Case 1) had chronic cor pulmonale. Two (Cases 2 and 3) had hypertensive, and 3 (Cases 4, 5 and 6) arteriosclerotic heart disease. Six patients (Cases 7, 8, 9, 10, 11 and 12) had rheumatic heart disease. Case 13 had calcific constrictive pericarditis and auricular fibrillation. The diagnosis in Case 14 was chronic adhesive pericarditis with calcification, auricular fibrillation and a question of chronic interstitial myocarditis. One patient (Case 15) had idiopathic myocarditis. The clinical data are presented in Table 1.

TABLE 1 (*Concluded*).

Case No.	Control Period	Duration of Treatment with Neohydrin	Dose*	Result	Toxicity
		mo.	*tablet/day*		
9	Duration of 36 mo.; Thiomerin in 2-cc. doses 2 or 3 times weekly; frequent complaints of breathlessness, paroxysmal nocturnal dyspnea and chest pains; basal rales present.	3	3	Prompt response, with disappearance of all complaints at end of 1st wk.; 1.5 cc. of Thiomerin given once; no subjective complaints, though basal rales persist.	None
10	Duration of 81 mo.; digitalis for 5 yr.; Thiomerin, 2 cc. given 2 or 3 times weekly for 10 mo.; some symptoms of failure persisted; STO, 7 tablets 6 days weekly started, with adequate compensation; Thiomerin not required while patient on STO; no toxic manifestations from STO.	4	7	Adequate compensation; patient remarked appetite had improved since taking of Neohydrin.	None
11	Duration of 44 mo.; digitalis and parenteral mercurial diuretics, 2 cc., given once weekly for 20 mo.; cation-exchange resins tried for few wk. but omitted because of poor toleration; for 11 mo. mercurial diuretics given parenterally in 2-cc. doses twice weekly, symptoms of failure persisting; on STO, 7 tablets 6 times weekly for 2 mo., definite improvement though occasional injection of mercurial diuretic required; STO omitted for 4 wk., with rapid development of severe failure; STO resumed in same dose as previously, with improvement.	6	7	Within 1 wk. of start of Neohydrin therapy marked improvement noted, and parenteral diuretics not required; no symptoms subjectively or objectively.	Abdominal cramps occurred briefly periodically; symptoms cleared up each time in spite of continuation of Neohydrin; at one time gingivitis, abdominal cramps and diarrhea developed; Neohydrin omitted for 1 wk. then resumed; during this wk. with improved oral hygiene gingivitis cleared up; no recurrence of toxic symptoms.
12	Duration of 4 mo.; Thiomerin, 2 cc. subcutaneously once weekly, maintained compensation at fair level, but on occasion symptoms increased, requiring hospitalization.	11	7	Thiomerin, 2 cc. twice weekly, required during 1st 3 mo.; then none for next 2 mo.; Thiomerin twice in following mo.; then none for next 2 mo. failure increased; patient hospitalized and diagnosis of malnutrition with low hematocrit made; improvement with administration of packed red cells; patient now on periodic administration of Thiomerin in addition to Neohydrin.	None
13	Duration of 48 mo.; pericardiectomy done shortly after onset of failure 4 yr. before; failure persisted after operation and in spite of parenteral mercurial diuretics given once weekly.	5	4	Good result shortly after onset of treatment; no further evidence of failure subjectively or objectively.	None
14	Duration of 48 mo.; parenteral mercurial diuretics once or twice weekly; pericardiectomy 2 mo. before Neohydrin started; 3 wk. postoperatively severe failure (no medication); bilateral pleural effusions; edema +++; 16 lb. gained.	6	3	Within few days of start of Neohydrin pleural effusions disappeared; patient returned to dry weight; 1 mo. later, omitted Neohydrin for 6 wk. & gained 15 lb.; rt. pleural effusion developed; since Neohydrin resumed adequate compensation maintained.	None
15	Duration of 6 mo.; no ammonium chloride; brief trial of cation-exchange resin without effect; parenteral mercurial diuretics 2 cc. 2 or 3 times weekly; constant state of moderately severe decompensation.	1½	6	Fair results; necessary to give 2 or 3 cc. of mercurial diuretics parenterally weekly; after first 2 wk. weight remained constant and patient fairly comfortable; at end of 6 wk. became severely decompensated and died suddenly in hospital.	None

*For 6 days weekly.

DISCUSSION

Results with Neohydrin were good in 13 of the 15 cases studied.

In Case 9 the results were considered good in spite of the persistence of basal rales. All the disabling symptoms disappeared a few days after the start of Neohydrin therapy. The improvement in well being and morale was striking.

In Case 4 the results were regarded as good because, in spite of the periodic development of toxic symptoms, compensation was maintained.

Neohydrin was only fairly effective in Case 15, since parenteral injections of mercurial diuretics were required, though less frequently than during the control period.

The results in Case 12 were considered poor, since the patient required parenteral therapy frequently.

Case 8 demonstrates the axiom that routine therapy may not always bring about the desired results. Inadequate diuresis was obtained with the usual maintenance dose of digitalis (0.1 gm.) and with 5 tablets of Neohydrin daily. However, when the dose of digitalis was increased to 0.2 gm. daily, excellent diuresis with good compensation resulted, and only 3 tablets of Neohydrin were required.

Case 14 provided good evidence of the effectiveness of Neohydrin. Compensation, once obtained, was followed by recurrence of marked failure when the drug was omitted for six weeks. Compensation promptly returned after Neohydrin was resumed.

In 8 cases the patients had remained in decompensated states throughout the control period despite the use of cation-exchange resins and frequent injections of mercurial diuretics. However, after the administration of Neohydrin adequate compensation was obtained without further recourse to parenteral therapy.

In 3 cases (Cases 4, 7 and 11) in which the degree of failure was marked and cardiac reserve obviously low the starting dose of Neohydrin was more than 3 tablets. In all cases, if symptoms or signs of failure persisted, the dose of Neohydrin was increased, in some within a week, and in others after several weeks. The patient's response to therapy determined the rate at which the dose was stepped up.

STO contains the equivalent of approximately three times as much mercury as Neohydrin, as pointed out above. Notwithstanding this difference, the results with Neohydrin in 5 cases were as good as those with STO. In 4 cases the results with Neohydrin were better. In no case were the effects of STO superior to those obtained with Neohydrin. The average weekly dose of Neohydrin was even less than that of STO — 30 tablets of Neohydrin (equivalent to 300 mg. of mercury) as compared with 39 tablets of STO (equivalent to 1236.30 mg. of mercury).

Acute renal disease, such as acute glomerulonephritis, and chronic renal disease with insufficiency have always been considered contraindications to the use of mercurial diuretics regardless of the method of administration. No such contraindications were found in this study. However, most of the patients gave evidence of the type of kidney involvement frequently found in severe congestive heart failure. The findings were those of a congested kidney with normal function. These abnormalities were not considered to contraindicate the oral use of mercurial diuretics.

Damage to the renal tubular epithelium from prolonged use of mercurial diuretics has been mentioned occasionally in the literature. This complication was not seen in the cases studied in the cardiac clinic. According to Ray and Burch[7] mercury may be given in amounts adequate to achieve diuretic effect without apparent injury. These authors further state, "Renal function tests and histologic examination of the kidneys in subjects who had received large quantities of mercurial diuretics have rarely revealed any damage."

There have been no reports of fatal toxic reactions of the cardiovascular system with the oral use of mercurial diuretics, such as the cases that have followed the parenteral administration of mercury.

The most common manifestations of the toxic effects of orally administered mercurial diuretics are gingivitis, nausea, vomiting, abdominal pains, diarrhea and blood in the stools. It has been the experience of most investigators in this field that when the drug is discontinued there are no residual untoward reactions. If any distressing symptoms recur after the diuretic has been resumed it should be omitted.

In the present study 4 patients had toxic manifestations with Neohydrin similar to those observed during the oral administration of other mercurial diuretics. In only 1 (Case 4) was it necessary to omit Neohydrin completely because of the frequent recurrence of nausea and vomiting; this patient had had the same symptoms when she was given STO. In 3 cases gross blood was found in the stools on only one occasion. No significant reason for the bleeding could be detected. In each case, in spite of continued use of Neohydrin, there was no further evidence of bloody stools. Most of the toxic symptoms were mild and tended to disappear without cessation of therapy (Table 1). Annoying gingivitis responded promptly to improvement of oral hygiene.

More significant than mercurialism and more frequently encountered with the constant use of mercurial diuretics are the symptoms associated with excessive diuresis. These dehydration syndromes, manifested primarily by potassium deficiency, with resultant cardiac depression, and by sodium depletion, with its associated weakness, muscle cramps, abdominal colic, nausea, vomiting, fever and coma, must be watched for constantly and promptly treated. Electrolyte imbalances should be corrected before further diuresis is considered. In the present study with Neohydrin none of the clinical syndromes associated with excessive diuresis developed.

Hematologic and urinary findings were unchanged during the entire period in which the patients received Neohydrin.

Summary and Conclusions

Fifteen patients with severe congestive heart failure associated with various types of heart lesions were treated with Neohydrin.

Neohydrin proved to be an excellent diuretic in the treatment of chronic congestive heart failure. With only few exceptions, the drug completely replaced parenteral administration of mercurial diuretics. In several cases normal compensation was achieved with Neohydrin whereas less than adequate compensation had been obtained with much larger amounts of mercury given parenterally.

The dosage of Neohydrin must be individualized.

Toxic manifestations were occasionally noted, but in only 1 case were they severe enough to prevent further use of the drug.

Comparison of the relative effects of Neohydrin and another orally administered mercurial diuretic, Salyrgan-theophylline Oral (STO), is described.

Neohydrin was superior to STO in most cases in the completeness with which it relieved the congestive state and in the maintenance of compensation. This was considered significant in view of the relatively small amount of mercury contained in Neohydrin as compared with STO.

References

1. Stroud, W. D., Laplace, L. B., Wagner, J. A., and Miller, I. B. Clinical experience with Mercurital, oral mercurial diuretic in ambulatory patients. *Pennsylvania M. J.* 53:953-956, 1950.
2. Finch, G. H. Clinical investigation of tablet Neohydrin, new oral mercurial diuretic. *J. Iowa M. Soc.* 42:490-496, 1952.
3. Greiner, T., et al. Human assay of three new mercurial diuretic agents: promising preparation for oral use. *Proc. Soc. Exper. Biol. & Med.* 80:117-121, 1952.
4. Goldman, B. R., and Steigmann, F. Experience with new oral mercurial diuretic. *J. Lab. & Clin. Med.* 40:803, 1952.
5. Moyer, J. H., Handley, C. A., and Wilford, I. Results over two-year period on three experimental diuretics administered orally to patients with cardiac failure. *Am. Heart J.* 44:608-614, 1952.
6. Abramson, J., Bresnick, E., and Sapienza, P. L. Treatment of congestive heart failure in ambulatory patients with Salyrgan-theophylline administered orally. *New Eng. J. Med.* 243:44-47, 1950.
7. Ray, C., and Burch, G. E. Clinical aspects of mercurial diuretics. *Circulation* 3:926-937, 1951.

BOSTON MEDICAL LIBRARY

Report of the Librarian*

Henry R. Viets, M.D.

BOSTON

THE Librarian herewith presents his annual report, the fifteenth accounting of the state of the Library since he took office in 1938. This report covers the calendar year 1952, a year of increased use of the books and journals, with more readers than at any time in the last five years. The circulation of the contents of the Library reached an all-time high of 71,149, about two thirds of this number being used in Holmes Hall and one third outside the Library building. Thus, service to users not coming to the building amounted to 23,931 items, these books and periodicals being delivered by messengers, ambulances, express, mail and by our own efforts to hospitals, medical schools, individuals, clinics, nonmedical libraries and professional members. The business of collecting, assembling, making deliveries and discharging and reshelving on return, with the associated telephone messages and mail requests, made Holmes Hall, with its small reference-library staff, a center of continuous activity, a fact not fully realized by the fellows of the Library who never or only infrequently come to the building at 8 The Fenway. The catalogued books and pamphlets received during the year added over 3350 pieces of available medical literature, so that the year closed with 218,634 volumes and 155,642 pamphlets on the shelves and a vast accumulation of partly unsorted material in the basement, awaiting additional stacks to hold it in usable form. In addition to the books housed in the Harvard Deposit Library and a storage warehouse, more space was acquired outside the building by taking advantage of some empty stacks in the American Academy of Arts and Science, rented to the Library at a favorable rate for temporary storage. The books housed there, as well as those in the Deposit Library, can be made available when called for, so the Library now has two "live" extensions, a useful arrangement on what is hoped to be a temporary basis.

Fifty additional periodicals were acquired in 1952, 15 of them being published for the first time during the year. About 300 new books were received for review from the *New England Journal of Medicine*.

The Director, James F. Ballard, completed sixty years of association with the Library on October 24, 1952.

Accessions

Incunabula

Three broadside almanacs were added: *Almanach auf das Jahr 1471*, in German (Augsburg: Günther Zainer); *Almanach auf das Jahre 1487*, in German (Würzburg: Georg Reyser, 1487); and Faber von Budweis, Wenzel: *Almanac ad Leipzig ad annum*

*Presented at the annual meeting of the Boston Medical Library, May 18, 1953.

1492, in Latin. (Leipzig: Martin Landsberg). The first is thought unique (G. W. Ergänzungen und Verbesserungen. Band I-IV: 1288/20). The top and right margins are shaved. Of the second, only one complete copy is known; the Library broadside has two half-lines missing where it has been folded, and a few words and letters in the text. It is partly printed in red (G. W. 1420). The last (G. W. 9554) is one of a long series of almanacs issued by Faber von Budweis from 1487 to 1501. The Library has another by the same author, for the year 1496, in German (G. W. 9562) and his *Tables of the sun and moon* (Leipzig, 1494 [Klebs 388.1]).

In addition to the three almanacs, four printed books, issued before 1501, were purchased: *Legenda Alberti Magni* by Rudolphus de Novimagio (Cologne: before 1484, [Stillwell R334]); *Trutina rerum coelestium et terrestrium* by Joannes Abiosus (Venice: Joannes Rubeus Vercellensis, after February 5, 1498 [Stillwell A8]); *Dialogus in astrologiae defensionem cum vaticinio a diluvio ad annos 1702*, by the same author (Venice: Franciscus Lapicida, October 20, 1494 [Stillwell A7]); and *Arbor scientiae* by Raymund Lull (Barcelona: Pedro Posa, August 22, 1484 [Stillwell L344]). The *Legenda* contains a bibliography of the writings of Albertus on theology and philosophy. Lull's *Arbor scientiae* is a particularly fine copy, with the first leaf supplied in perfect facsimile.

Sixteenth-Century Books

More than 120 books published in the sixteenth century were acquired. Among them was a famous book on gout, *Liber de Podagra, et id Genus Morbis* (Paris: Guil. Morelium, 1558), by Demitri Pepagomeni and dedicated to Michaëlem Palaeologum. An edition in Greek was issued by the same printer at the same time and place, so that learned colleagues in Paris could read it in the author's original language. In the Library copy both editions, finely printed, are bound in the same volume. Of more interest is the fact that the book was published in 1558, although written by a Greek physician of Constantinople in the thirteenth century and dedicated to his emperor, Michael Palaeologus, presumably one of his gouty patients, who restored the decadent Byzantine Empire to some of its former glory, reigning as Michael VIII from 1261 to 1282. Demetrios Pepagomenos composed an outstanding treatise for the new scholarly world of Byzantine culture under the direction of the Palaeologi, many of whom were distinguished for their humaneness and erudition. Written before 1282, the text of Demetrios must have found its way out of Constantinople before the final conquest by the Turks in 1453, five hundred years ago, a date usually considered as the beginning of the modern age.

The manuscript was translated into Latin by Marcus Musurus and first printed by Janus Lascaris, at Rome in 1517, so that the 1558 editions acquired by the Library are the second printing. The Library also has a French translation, by Frédéric Jamot, *Traicté de la Govtte* . . . (Paris: Ph. G. De Roville, 1567); another edition (Paris: Galiot du Pré, 1573) and finally a new translation into both Greek and Latin, by Joh. Steph. Bernard (Lugduni Batavorum: Philippum Bonk, 1743).

Demetrios wrote a sensible book at a time when Greek medical writings were few and generally sterile. He considered gout as a constitutional disease caused by incomplete elimination of excrets. He therefore treated his patients by purgation, using a pill of aloes.

Gout. The disease was known in animals before 500 B.C.; in man, it was described by Hippocrates, as podagra, or seizure of the foot. The words, gout and podagra, became interchangeable about the time that Demetrios wrote his book. The *Oxford English Dictionary* notes, as of 1290,

> In his fot ane hote goute, that poudagre icleopeod is.

and by 1300:

> The gutte the potagre es it to bete,
> It fell al dun in-til his fete.

The word, gout, from the Latin, *gutta*, indicates the idea of the dropping of morbid material about a joint. James Russell Lowell said that it was not Latin at all, but simply a term indicating the patient's inability to "go out."

The history of gout has not been fully investigated, and the literature is scattered. A definitive monograph would be of value. Mr. Colby, the reference librarian, has provided me with a few references. Klibanoff,[1] in his Berlin dissertation, partly covered the period from Hippocrates to Paracelsus, and Albert[2] the seventeenth and eighteenth centuries. Of the more recent accounts, Schnitker[3] wrote an excellent review in 1936; Hormell[4] added some notes in 1940, and Neuwirth[5] a brief but scholarly documented summary in 1943. Neuwirth points out that although Ralph Bocking (Radulphus) is credited with first using the term *gutta* in his biography of St. Richard of Wyche, bishop of Chichester, composed about 1270, Villehardouin, writing between 1207 and 1212, used the words, *une grant maladie de gote* and *gutta* is traced to the tenth century. Demetrios' account does not appear to have been known to Hormell, Neuwirth or Schnitker.

Demetrios is remembered, however, more for his book on the feeding and nursing of hawks[6] than for his treatise on gout (Sarton considers it one of the earliest books on falconry in Christian Europe). In addition to abundant information on everything that a good falconer ought to krow, there is a section on helminthology as it relates to hawks. Casey Wood[7] praises it highly.

Cutis hyperelastica. The Ehlers–Danlos syndrome was described by Edvard Ehlers as *cutis laxa* in 1901, and by Danlos under the same name in 1908. Danlos added three other symptoms to his syndrome: hyperlaxity of the joints, fragility of the skin and pseudotumors following trauma. India-rubber skin, however, was recognized long before 1901 by the Dutch surgeon, Job Jansz VanMeek'ren (1611-1666), and figured in his book, published in Amsterdam in 1668. The original Dutch edition was translated into German and published in Nürnberg in 1675 and into Latin and issued in Amsterdam in 1682. The Amsterdam imprint was translated into Latin by Abraham Blaes, a medical student, the son of the famous comparative anatomist, Gerard Blaes (Blasio), who was also interested in anatomical curiosities. It is a copy of the last book that is in the Library (Fig. 1).

Men with elastic skin have often been exhibitionists, as noted by Gould and Pyle. One in Budapest possessed great elasticity in the skin of his whole body; even his nose could be stretched. Some, as noted by Danlos, could bend the fingers backward and forward. Meek'ren's life and works are noted in articles by R. Krul[8] and E. D. Baumann.[9] In addition to describing the elastic skin, Meek'ren (also frequently spelled Meekeren or Meekren) was the first to record a bone-graft operation, transplanting a piece of bone from a dog's skull into a cranial defect in a soldier. Although healing was perfect, the church ordered him to remove the portion of bone.

To the "pest" tracts there were added Nicolo Massa's *Liber de Febre Pestilentiali* (Venice, 1556), in a volume of collected tracts, with contemporary vellum binding and clasps intact; Johan Widmann's *Regimen . . . wie man sich in pestilentzischem lufft halten soll* (Strassburg, 1511); and Robert Gropertius' *Regimen Sanitatis* (Ghent: 1538).

The translation into German of Widmann's plague tract is dedicated to his three daughters. The Library also has the first edition of this same work, printed in Strassburg in 1497, as described, with a note on the author's life, in the "Report of the Librarian" for 1948. Robert Gropert, a Netherland physician, whose portrait appears on the titlepage of this book, was also known as Cropetius. He published another tract on the pest, issued in Paris in 1539.

Also acquired were Nicolo Massa's *Epistolae medicinales* (Venice, 1550), Nicolas Goddin's *La chirurgie militaire* (Antwerp, 1558) and Symphorien Champier's *De omnibus morborum generibus* (Basel, 1547).

Goddin (1509–?), or Godin, was born and practiced in Arras, a city of wealth and culture in northern France, early in the sixteenth century. Although famous for its tapestries, Arras was also a military center in the Pas de Calais. Here Goddin wrote *La chirurgie-practique de maitre Jean de Vigo* (Paris, 1531) in addition to *De Chirurgia militari*, the French translation of which the Library has just obtained. The book is the second edition of the translation, the first having been published in Ghent in 1553. It deals only slightly with military surgery, but treats of the pest and dysentery, important diseases in the wars of his time. In the military part there are a series of chapters on errors

FIGURE 1. Observationes Medico-Chirurgicae. *By Jobi à Meek'ren.* (*Amsterdam, 1682.*)

committed by surgeons, along with Goddin's vigorous complaints against the charlatans and empirics of his time. He was a contemporary of Paré, who entered on his career as a military surgeon in 1536, but Goddin seems to have acquired practically nothing of the spirit of the Renaissance having bogged down at his classical level of ignorance, unaware of the new awakening stimulated by Vesalius (1543) and Paré. His best observations are in the last chapter, where he deals with the or-

ganization of a military camp and the prevention of contagion from overcrowding and poor sanitation, but the heavy hand of medievalism directed his treatment of infections and the soldiers were freely bled and dosed with white vitriol (zinc sulfate) and black copper (monoxide) to the point of exhaustion.

The Champier volume adds another to the growing list of works by this author (Table 1). The Library also has another book, attributed by some to Champier, *Evangelistarum Symphonia de lazero martha et maria* (Venice: Joan Phiroben & Joan Divineur, November 23, 1519).

TABLE 1. *Books by Symphorien Champier (1472-1539) Now in the Boston Medical Library.*

Campus Elysius Gallice amoenitate refertus
8°. pp. 8,135,5. Lyons: Melchior & Gaspar Trechsel, 1533.
Idem.
8°. pp. 8,135,1. Lyons: Melchior & Gaspar Trechsel, 1543.
Castigationes seu emendationes pharmacopolarum. Officina apothecariorum
8°. fol. CXII; LV, 1. Lyons: Joan Crespin, 1532.
Cathegorie medicinales
8°. fol. 40 Lyons: Johan Marion, 1516.
Cribratio: lima: & annotamenta in Galeni Avicennae & conciliatoris opera
8°. fol. LXXII. Paris: Jodocus Badius Ascensius, 1516.
Cribratio medicamentorum
8°. pp. 115,1. Lyons: Seb. Gryphium, 1534.
Horus Gallicus
8°. pp. 12,83,1. Lyons: Melchior & Gaspar Treschsel, 1533.
Idem.
8°. pp. 12,83,1. Lyons: Melchior & Gaspar Trechsel, 1543.
Index librorum in hoc volumine contentorum. De Medicina clarii
8°. fol. VI, LX; XXIV, II; XXIV, II; VIII; XXVIII, II; XXVIII. Lyons: Jaannot de Campis, 1506.
Index librorum qui in hoc volumine continentur mirabilium divinorum humanorumque volumina quattuor
8°. fol. LVI; XLIV; XXIV; XXVI. Lyons: Jacob Mareschal, 1517.
Medicinale bellum inter Galenum et Aristotelem geratum.
8°. fol. 24. Lyons: Johan Marion, 1516.
De omnibus morborum generibus
8°. pp. 48,639,1. Basel: Henrich Petrum, 1547.
Periarchon
8°. pp. 63,1. Lyons: Melchior & Gaspar Trechsel, 1533.
Idem.
8°. pp. 63,5. Lyons: Melchior & Gaspar Trechsel, 1543.
Practica nova in medicina
8°. fol. IV, CXLIX. Lyons: unknown printer, not before 1504.
Idem.
8°. fol. CLII. Lyons: Johan Marion, 1517.
Idem.
8°. fol. 51. Venice: Octavianus Scotus, 1522.
Pronosticon libri tres quorum primus
4°. fol. XII. Lyons: Vincent de Portonaris, 1518.
Qui hoc in volumine tractantur
Epithome commentariorum Galeni in libros Hippocratis cohi
8°. fol. 120. Lyons: Johan Marion, 1516.
Qui in hoc opusculo habentur
Duellum epistolare
8°. fol. 96. Venice: Joan Phiroben & Joan Divineur, 1519.
Rosa Gallica aggregatoris
8°. fol. VIII, CXXXVI. Paris: Jodoco Badio, 1514.
Idem.
8°. fol. VIII, CXXXVI. Paris: Jodoco Badio, 1518.
Speculum Galeni
8°. fol. CCXXXII. Lyons: Joan de Jonvelle, about 1512.
Symphonia Platonis cum Aristotele & Galeni cum Hippocrate
8°. fol. CLXXII. Paris: Jodoco Badio, 1516.
De triplici disciplina cuius partes sunt
8°. fol. XXIV; CIV; CVIII; XLVIII. Lyons: Claude Davost, 1508.
De monarchia Gallorum campi aurei: ac triplici imperio . . .
4°. fol. XXII, XXX, XVIII. Lyons: Melchior & Gaspar Trechsel, 1537.

Miscellaneous

As in past years, a large number of books, periodical files and other material of medical interest came from the many friends of the Library. Notably were the gifts from the American Optical Company, the Carnegie Institute, the Forsyth Dental Infirmary, the John Hancock Life Insurance Company, the Massachusetts departments of Education, Industrial Accidents and Public Health, the New England Life Insurance Company, various hospitals and medical schools, the *Journal of Bone and Joint Surgery* and the *New England Journal of Medicine*. Individual donations came from Mrs. Doris Appel, Mrs. Arthur D. Little and Drs. Dennistoun Bell, J. B. Bruce, Henry F. Howe, Franc D. Ingraham, James C. Jenney, Harris P. Mosher, Fritz B. Talbot and others. Dr. Talbot added to his special collection a number of rare books, and Dr. Janney gave us his medical library. The Harvard Medical School Library, as in the past, gave a large number of books, pamphlets and periodicals, with their collection of dissertations and theses.

EXHIBITIONS

Exhibits were displayed on "Boston Medicine, 1643–1926"; "Important Events in Medicine Fifty Years Ago"; "Broadside almanachs, 1470–1499: Calenders, 1500-1551"; "Books on Food and Diet, 1481-1576"; and "Ramon y Cajal, 1852-1952."

MEETINGS

Meetings of the Biohistorical Club, Boston School of Occupational Therapy and Boston Medical History Club were held in the Library.

PUBLICATIONS

Phippen, W. G. Boston Medical Library: report of president. *New Eng. J. Med.* 247:76, 1952.
Viets, H. R. Boston Medical Library: report of librarian. *New Eng. J. Med.* 247:430-434, 1952.
Idem. Boston Medical Library: report of librarian, Part II: Medicohistorical activities in 1951. *New Eng. J. Med.* 247:492-496, 1952.
Idem. Charles Scott Sherrington, 1857-1952: an appreciation. *New Eng. J. Med.* 246:981, 1952.
Idem. Van Riebeeck and Cape Town. *New Eng. J. Med.* 246:503, 1952.
Ballard, J. F. Physician orators of Boston. *New Eng. J. Med.* 247:646, 1952.
Editorial. Benjamin Rush in Edinburgh. *New Eng. J. Med.* 246:241, 1952.
Editorial. Corti and his research. *New Eng. J. Med.* 246:428, 1952.
Editorial. Medical bookplates. *New Eng. J. Med.* 246:558, 1952.
Editorial. Isaac Ray Medical Library at Butler Hospital. *New Eng. J. Med.* 246:672, 1952.
Editorial. National Medical Library. *New Eng. J. Med.* 247:415, 1952.
Editorial. Ex Libris: James F. Ballard. *New Eng. J. Med.* 247:740, 1952.
Boston Medical Library. Science librarians. *New Eng. J. Med.* 246:202, 1952.
Nobel prizes. *New Eng. J. Med.* 246:276, 1952.
Benjamin Rush as a spirit. *New Eng. J. Med.* 246:314, 1952.
Boston Medical Library note. *New Eng. J. Med.* 246:472, 1952.
Conan Doyle and Sherlock Holmes. *New Eng. J. Med.* 246:672, 1952.
The great plague. *New Eng. J. Med.* 246:517, 1952.
Miguel Servet. *New Eng. J. Med.* 246:517, 1952.
Notes. *New Eng. J. Med.* 247:375, 1952.
Foundations of biography. *New Eng. J. Med.* 247:657, 1952.
Tomas Romay. *New Eng. J. Med.* 247:695, 1952.
Medical stamps. *New Eng. J. Med.* 247:742, 1952.

REFERENCES

1. Klibanoff, M. *Zur Lehre der Gicht in geschichtlicher Beziehung von Hippokrates zu Paracelsus. 22 pp. Berlin: H. Blanke, 1912.*
2. Albert, H. *Beiträge zur älteren Lehre von der Gicht im 17. und 18. Jahrhundert.* 65 pp. Berlin: H. Blanke, 1911.
3. Schnitker, M. A. History of treatment of gout. *Bull. Inst. Hist. Med.* 4:89-120, 1936.
4. Hormell, R. S. Notes on history of rheumatism and gout. *New Eng. J. Med.* 223:754-760, 1940.
5. Neuwirth, E. Milestones in diagnosis and treatment of gout. *Arch. Int. Med.* 72:377-387, 1943.
6. Demetrius Constantinopolitanus. *De cura et medicina accipitrum.* 527 pp. Lugduni: G. Rovillium, 1562. Also (Greek text) in: Rigaltius, N. *Rei accipitrariae scriptores.* Lutetia: H. Drouart, 1612.
7. *The Art of Falconry Being the* De arte venandi cum avibus *of Frederick II of Hohenstaufen.* Translated and edited by C. A. Wood and F. M. Fyfe. 637 pp. Stanford University: Stanford University Press, 1943.
8. Krul, R. Job van Meekeren. *Geneeskund. Courant.* 53: No. 18. April 30, 1899.
9. Baumann, E. D. Job van Meekren. *Nederl. tijdschr. v. geneesk.* 67: 456-479, 1923.

MEDICAL PROGRESS

TREATMENT OF ANGINA PECTORIS*

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MORGAGNI,[1] in the middle of the eighteenth century, described patients who were no doubt suffering from angina pectoris; however, it remained for Heberden,[2] in 1768, to present his classic description of the disorder:

> But there is a disorder of the breast marked with strong, peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare which deserves to be mentioned here at length. The seat of it, and the sense of strangling and anxiety with which it is attended, may make it improperly called angina pectoris. . . . They who are afflicted with it are seized while they are walking (more especially if it be uphill and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life if it were to increase or to continue, but the moment they stand still all this uneasiness vanishes.

His analysis and report of over 100 cases is so accurate and detailed that he is justly referred to as the pioneer in the field of coronary-artery disease. Jenner,[3] a few years later, noted the relation of angina pectoris to heart disease. During the succeeding decades no important contributions appeared except for a few anatomic studies of the coronary vessels. In 1912, Herrick[4] presented in the American literature a description for the first time of sudden coronary occlusion.

ANATOMY OF PAIN PATHWAYS

The innervation of the heart is provided by the autonomic nervous system through the sympathetic and parasympathetic (vagus) fibers. The nerves supplying the heart are mixed and transmit both motor or "effector" impulses and impulses via sensory or afferent fibers. Cardiac pain represents referred pain from the heart in which the impulses pass via the afferent sympathetic fibers to their respective ganglions, located in the cardiac plexus, which consists of a meshwork of nerves and ganglions situated at the base of the heart about the arch of the aorta. From there, pain fibers pass to the paravertebral ganglionated chains on each side via the middle and inferior cardiac nerves and the upper four or five thoracic nerves. Afferent impulses then enter the dorsal roots of the spinal nerves and make their final synapse in the substantia gelatinosa of the spinal cord. Pain at a conscious level is referred to the area supplied by the spinal nerve. Because pain impulses traverse mainly the sympathetic fibers, surgical attacks on angina pectoris have been confined largely to that system.

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MEDICAL TREATMENT

Nitrites

Voegtlin and Macht,[5] working on isolated arterial strips, and Meyer,[6] working on the intact heart, first noted the ability of nitroglycerin to produce dilatation of the coronary artery. Other studies[7, 8] have confirmed these original observations. Its action in human beings may be related in part to reduction in peripheral vascular resistance[9] and inhibition of sympathicomimetic substances liberated by an anoxic myocardium.[10] Nitroglycerin, first introduced in 1879 by Murrell,[11] has remained the most reliable preparation in the treatment of angina pectoris. In fact, the response to this drug has been utilized by many as a diagnostic test for Heberden's syndrome. Gold[12] noted improvement in 82 per cent of 60 patients treated with this preparation, and Wayne and Laplace[7] reported a reduction in the time of onset of pain in 10 of 11 patients with coronary-artery disease after the performance of a standard exercise-tolerance test. The value of nitroglycerin as a prophylactic was first stressed by Leech[13] in 1893, and re-emphasized by Levy[14] some years later. The longer-acting nitrite preparations have recently been revived but have never assumed a great popularity because of the unpleasant side reactions, including intractable headache. The newest of these preparations is pentaerythritol tetranitrate. In average doses of 10 mg. three times a day before meals, according to Winsor,[15] a satisfactory improvement in the frequency of precordial pain was obtained in 78.4 per cent of 125 patients suffering from angina pectoris. The drug seems to be relatively nontoxic in two or three times the dose necessary to produce maximal therapeutic effects.[16] Russek[17] found it to be the most useful drug available today when continuous prophylactic oral therapy is desired in angina pectoris.

Xanthines

Although the xanthines have been employed for over fifty years in the treatment of angina pectoris, their efficacy is still in dispute. Askanazy,[18] in 1895, first recognized the ability of these preparations to relieve anginal paroxysms. In 1935, Fowler, Hurevitz and Smith[19] noted that after ligation of coronary vessels in dogs and subsequent intravenous injection of aminophylline, the zone of infarction became smaller, and the degree of cyanosis at the margins lessened. Laubry[20] and others have con-

firmed this work; the vasodilatory action becomes maximal in five to twenty-five minutes.[21] The direct myocardial stimulation produced by the xanthines probably has few therapeutic implications though cardiac output is increased up to 30 per cent.[22] In carefully controlled studies of 227 patients, both Gold[23] and Master[23] concluded that patients with angina pectoris were unable to detect differences between the effects of xanthines and suitably disguised placebos. Likewise, the efficacy of such therapy has been questioned by Evans and Hoyle.[24] However, Riseman and Brown,[25] employing the exercise-tolerance test, observed that 59 per cent of 17 patients treated with these drugs could withstand more physical exertion without experiencing pain. Others[26, 27] have reported some degree of improvement. Levy[28] employed the anoxemia tests to evaluate the benefit of aminophylline in angina pectoris. On oral administration there was a prolongation of 26 per cent in the time of appearance of pain, as compared with 63 per cent with the intravenous route. Likewise, ST-segment depression occurred earlier in the former group. In general, one can conclude, as Boyer did,[29] that the benefit from these drugs is variable. The Council of Pharmacy of the American Medical Association recently stated that the clinical evaluation of the usefulness of the xanthines in the treatment of angina pectoris is still far from satisfactory.

Papaverine

This is a nonhabit-forming opium derivative of the benzyl isoquinoline group first suggested for the treatment of angina pectoris by Pal[30] in 1913. Essex and his associates,[31] employing trained unanesthetized dogs, confirmed the earlier finding of Anrep[32] that papaverine is a powerful coronary vasodilator. Katz[33] found it useful in 12 out of 17 patients with angina pectoris treated with doses of 0.1 gm. four times a day. More recently, others[34, 35] have been less impressed with results obtained. Rinzler[36] states that its administration is not without dangers, among which are toxic arrhythmias. The effects of the synthetic analogue of papaverine, paveril, have been studied by Scott[37] and found to produce little subjective or objective improvement in patients with angina pectoris, despite the low incidence of toxic reactions.

Androgens

In 1939 Edwards, Hamilton and Duntley[38] demonstrated by spectrophotometry that diminished arterial blood supply to the skin was increased after the administration of testosterone propionate. Subsequently, this hormone was given a trial in the treatment of angina pectoris, and some benefit was reported in over 70 per cent of cases.[39-44] Lesser[45] administered this preparation to 100 patients for periods lasting up to five years. He thought that 91 per cent improved on a regimen of 25 mg. twice a week for two weeks and then weekly for a total of 12 injections. He attributed the lack of success in some cases to insufficient treatment, since some showed no improvement until after the first month. Levine[46] treated 19 patients with angina for four weeks with androgens, and only 6 improved. Others, likewise, have reported unfavorably.[47, 48] Today, hormonal therapy is less commonly employed, owing to the high cost, the necessity for parenteral administration and the uncertain results obtained.

Khellin

The compound dimethoxy-methyl-furano-chromome (khellin) was isolated in 1930 by Fantl and Salem[49] from the seeds of *Ammi visnaga*, a plant that grows wild in Egypt. In concentrations of 1:200,000 it is said to cause a threefold increase in the coronary sinus outflow and to exert a vasodilator action four times that of aminophylline by mouth.[50] Its absorption is rapid, and effective blood levels are obtained within thirty to sixty minutes of oral administration.[51] It is slowly excreted and dissipated, and cumulative affects may consequently occur.[52] Utilizing the blind-test technic to evaluate the effect of khellin by mouth in a carefully selected group of 14 patients with angina pectoris induced by effort, Hultgren[53] noted that 7 patients experienced a reduction in the frequency of the anginal attacks as compared with similar periods of placebo administration. Anrep[54] claimed improvement in 140 of 250 patients treated with this drug, and Scott[55] noted subjective improvement in 11 out of 20 cases but mentioned that there was no decrease in the frequency of attacks. Others[56-59] have observed favorable results in a small series of cases. Gold,[60] however, employing the daily report-card method was not impressed with the benefit of the drug in controlled experiments. Likewise, Strong[61] treated 41 patients with anginal syndrome over a seventeen-month period and observed marked improvement in only 5 per cent.

One of the chief objections to this form of treatment is the high incidence of toxic reactions in doses of 40 to 240 mg. a day. Nausea, vomiting, anorexia, epigastric burning, dizziness and diuresis may develop. Conn[62] noted gastrointestinal symptoms in 62 per cent of 42 patients with the anginal syndrome, and the reactions were severe enough in 12 patients to require cessation of therapy. Recently, parenteral administration of visammin has been employed, with encouraging results though local reactions are common.[63] Better purification of the drug and establishment of a minimum effective daily dose seem desirable.[64, 65]

Medical Thyroidectomy

Clinically, alleviation of hyperthyroidism in many patients is accompanied by amelioration or even disappearance of angina pectoris. With this in mind investigators have attempted to produce hypo-

metabolism in euthyroid patients. Ben-Asher[66] reported that thiouracil was of benefit in 25 out of 37 patients with angina pectoris. Hollander[67] noted improvement in 4 out of 10 cases. Waitzkin[68] treated 7 cases of angina pectoris with propylthiouracil and observed significant relief of pain in 3 cases. He attributed the improvement to a decline in circulating thyroid hormone, rather than to general metabolic depression. However, the difficulty with the use of the thiourea derivatives is the inability to establish a constant hypometabolic state; in addition they may produce water retention and pulmonary edema.[69] Blumgart[70] has recently employed radioactive iodine therapy in 26 patients with angina pectoris. In doses of 26 to 206 millicuries this agent produced myxedema in the majority of patients during the next five weeks to six months. Therapeutic results were considered excellent in 9 cases (average follow-up period of twenty-seven months) and worth while in 10. Jaffe[71] has reported good results in 56 per cent of 95 patients treated in a similar way; likewise, Wolferth[72] has been impressed with this form of management of angina pectoris. The appearance of myxedema can usually be managed by small amounts of thyroid.

Anticoagulants

The observation that intravenous administration of heparin reduces alimentary lipemia was first made by Hahn[73] in 1943. Heparin in the treatment of angina pectoris was studied by Gofman,[74] who, by means of the ultracentrifuge, demonstrated that the plasma lipids are carried in the form of lipoproteins of varying molecular size. The S_f 12–20* group has been associated with atherosclerosis, and in human beings this spectrum is often reduced to normal by heparin.[75] The California group[74, 75] found that this anticoagulant given intravenously in doses of 50 to 100 mg. once or twice a week was of value in producing dramatic relief in 55 of 59 patients with angina pectoris. However, they could not always correlate the relief of pain with the effect of heparin on the serum lipids. Engelberg[76] administered similar doses of heparin for six to twelve months to 29 patients with this disease, with control periods of saline injections. Pain was relieved in 55 per cent of the cases, and there was often associated improvement in the pattern of the exercise electrocardiogram and the ballistocardiogram. Other investigators[77-80] could not duplicate these results in a study of 98 patients with angina pectoris, employing various control technics, in which heparin was administered in a similar fashion. Rinzler[81] utilized the double blindfold method to evaluate this method. Eighteen patients were selected for the study and paired on the basis of age, sex, duration of effort angina and incidence of myocardial infarction. They were then divided at random into parallel series. Heparin was then given to a group of 9 patients and a placebo to the other group. Heparin was given in doses of 100 mg. twice weekly for eight or nine weeks. The effect of the injections was judged by the patient's daily evaluation of cardiac pain and the average number of nitroglycerin tablets used each week. The results indicated the inefficacy of heparin in the control of pain. Of interest is the fact that the placebo (gelatin dextrose) caused a greater fall in the serum lipids of the S_f 20–100 than the heparin. However, anticoagulants appear to be of some benefit in patients who exhibit the clinical picture of impending coronary occlusion.[82, 83]

Ganglionic Blocking Agents

Acheson and Moe[84] showed in 1945 that tetraethylammonium ion improved the work capacity of the heart. Subsequent experiments cast doubt on the efficiency of this agent as a vasodilating agent.[85] However, previous experience with the use of paravertebral block indicated that an autonomic-ganglion blocking agent may be of value in interrupting the neurogenic reflex arc in angina pectoris. In 1950 Atkinson[86] treated 28 patients with tetraethylammonium chloride; 25 showed symptomatic improvement as judged by a decrease in the number of anginal attacks, and an increase in exercise tolerance. However, severe hypotension, dizziness and light-headedness, transitory metallic taste in the mouth and paresthesias in the hands and feet may develop. The optimal dose was determined by initial use of small intravenous injections of 50 to 100 mg. weekly, with a working up to the optimal dose. The patients were followed for six to twelve months, and no harmful effects from the use of this preparation could be noted.

Diet

It has not been conclusively shown that obesity predisposes to early coronary atherosclerosis.[87, 88] However, as Proger[89] has mentioned, there can be no doubt of the benefit of weight reduction in the patient with coronary-artery disease and angina pectoris. Gofman[90] has stated that control of obesity as a therapeutic measure in atherosclerosis gains support because of its close association with the atherogenic S_f 35–100 and S_f 12–20 lipoprotein particles. The relation of cholesterol intake to atherosclerosis has been the subject of many reports in the literature during the past few years, and no attempt is made to review these advances. It is sufficient to point out that a reduction in blood cholesterol requires a severe dietary restriction of both animal and vegetable fats.[91, 92] Of interest is the recent observation of Block and his associates[93] at the Mayo Clinic that obese patients with angina pectoris have a better prognosis than those who are not obese. This is contradictory to the general observations of Dublin and Marks,[94] and

*Molecules with a flotation (negative sedimentation) rate of 12 to 20 times 10^{-13} cm. per second per dyne per gram.

may be due, as the authors suggest, to a selectivity of patients that produces a spurious correlation.

Other Measures

Vitamin E therapy, initially received quite enthusiastically,[95,96] has now fallen into disrepute.[97-100] Baer,[101] in a review of the papers attesting to the beneficial effects of this vitamin, has commented on the uncritical manner in which the cases were presented, particularly the failure to take into account the natural history of the cardiac disturbance under consideration. Likewise, the early favorable report of the use of the enzyme Cytochrome C[102] in conditions associated with myocardial anoxia has not been confirmed.[103] Radiation therapy to the spine, originally proposed by Sussman,[104] was recently tried without success.[36] Raab[105] reported on the clinical course of 200 cases of angina pectoris treated with irradiation of the adrenal glands. The procedure was intended to decrease the abnormal secretory irritability of the adrenal medulla. Clinical improvement of all degrees was noted in 152 patients beginning on an average of four weeks after the start of therapy. The report is difficult to evaluate in view of the fact that cervical and thoracic x-ray treatment was given in addition to the adrenal irradiation in 28 per cent of the cases. The time-honored dictum that alcohol is an effective coronary vasodilator has been challenged by Russek.[106,107] Ethyl alcohol had no significant effect on the electrocardiographic response to standard exercise, as compared with nitroglycerin. However, the conclusion must not be drawn that a drug incapable of preventing the hypoxic changes on the electrocardiogram after exercise will likewise be ineffective in relieving the effort pain that a patient experiences. The fact remains that alcohol occasionally gives relief when the nitrites have failed.[108]

An interesting observation is that of Levine and Harvey,[109] who showed that stimulation of the carotid sinus, provided it results in definite slowing of the pulse, may rapidly lessen or completely relieve the pain of angina pectoris. This maneuver was successful in a series of 40 patients experiencing 50 attacks of angina pectoris, whereas in a control group of 60 patients with nonanginal pain it had effect in only 7. The frequency of immediate recurrence of pain after a short period of relief has caused Freedberg[110] to state that no significant change has occurred in the discrepancy between myocardial demand and blood supply as a consequence of carotid-sinus stimulation. Finally, it should be mentioned that a recent investigation suggests that inhalation of 100 per cent oxygen does not influence myocardial anoxia in patients with angina pectoris in whom the arterial saturation of oxygen is normal.[111]

Surgical Treatment

In view of the failure of the relief of angina pectoris by medical therapy, one is justified in considering surgical treatment when dealing with a patient who has frequent paroxysms of pain. It must be kept in mind that, although the pain may be persistent, the amount of organic disease of the heart is not necessarily great. Consequently, any surgical procedure that yields relief from attacks of angina pectoris and leads to rehabilitation of patients afflicted with this syndrome is worthy of consideration.

The surgical measures available for the relief of this disturbing disorder fall into three general groups: interruption of the pain pathways from the heart, improvement of the coronary circulation and thyroidectomy. The experience with each of these is considered separately.

Interruption of the Pain Pathways to the Heart

Sympathectomy

François-Franck,[112] in 1899, suggested thoracocervical sympathectomy for the relief of angina pectoris, though he did not perform the operation. However, it was not until 1916 that Jonnesco[113] first reported a cure of a case of angina pectoris by removal of the ganglionated cervical chain on the left side under local anesthesia. Cutler,[114] in 1927, reviewed the results of this type of operation and noted that relief was afforded in only about 50 per cent of patients. The reason for this was made clear when it was demonstrated that accessory pathways to the heart existed via the thoracic cardiac nerves. Subsequently, a surgical procedure was carried out that included excision of the stellate and the superior four or five thoracic ganglions. In 71 patients operated on by Lindgren and Olivecrona[115] the upper four thoracic ganglions were removed. Thirty-three left-sided operations and 34 bilateral operations were performed. Complete relief of pain was obtained in 44 per cent, and in 41 per cent partial but significant benefit was derived. Three patients died during the operation. Ray[116] operated on 10 normotensive and 28 hypertensive patients with angina pectoris, and noted uniform relief of pain in the former group. White and Bland[117] reported resection of the upper thoracic ganglions in 8 patients with angina pectoris. Unilateral procedures were done in 7 cases. There were 2 postoperative deaths in the series, the remaining patients experiencing varying degrees of relief. Evans and Poppen[118] reviewed their experience with 10 patients on whom thoracolumbar sympathectomy was performed. Bilateral procedures were done in all, and relief of angina pectoris was considered complete in 5 cases. Recently, Smithwick[119] and his group suggested that total transthoracic splanchnicectomy is of considerable value in the treatment of patients with angina pectoris and hypertension. Of 59 patients, 70 per cent of whom had severe angina pectoris, complete relief of pain followed the procedure in 57 per cent, and some degree of improve-

ment was noted in another 23 per cent. The operative mortality was 6.5 per cent. The results appear more impressive when one realizes that of 128 patients with angina pectoris and hypertension subjected to lumbodorsal sympathectomy, only 37 per cent noted any improvement, despite the fact that the angina pectoris was of a less severe type. A final group of 54 patients treated by medical means did the poorest, complete relief of pain being obtained in only 3 per cent and partial relief in 16 per cent.

Some disadvantages of sympathectomy in the treatment of angina pectoris are noteworthy.[113-115] In the first place 10 to 50 per cent of patients have pain in the neck or jaws for the first time after the operation. Secondly, this procedure will probably not relieve pain in the neck and jaw that is present preoperatively; in this regard, Olivecrona[115] has recommended injection of the mandibular nerve for this symptom. Thirdly, if sympathectomy is carried out, it must be a bilateral procedure, for pain on the opposite side may follow a unilateral sympathectomy. A history of myocardial infarction and the presence of congestive failure are serious contraindications.[116] Poppen[120] has stated that the likelihood of death or a poor result is definitely increased when lumbodorsal sympathectomy is performed on a patient with hypertension and angina pectoris.

Posterior Rhizotomy

This was first proposed by Danielopolu[121] in 1923 but was not actually carried out until 1936 by Davis and Pollock.[122] That such a procedure is efficacious is well attested to in the reports of a wide group of investigators, cited by White,[117] who noted relief of pain in about 95 per cent of patients with angina pectoris subjected to this type of operation. The operative mortality in these cases was 10 per cent. Though posterior rhizotomy is a formidable procedure, requiring laminectomy, it permits severance of cardiac afferent fibers on both sides at one operation.[122] Despite the fact that the problem of regeneration of nerve fibers is not present, dysesthesia and anesthesia occurring in the upper thoracic dermatomes have to be contended with postoperatively.[116, 117, 124]

Paravertebral Alcohol Injection

Chemical block of the pain pathways from the heart is the procedure of choice in patients with angina pectoris who are considered poor risks for more dramatic surgical attacks. Mandl,[125] in 1925, was the first to advocate this method of treatment. He reported 16 cases in which he injected 0.5 per cent novocain paravertebrally, with excellent results. A year later, Swetlow[126] reported prompt and satisfactory relief of pain in 8 patients. However, it remained for J. C. White[127] to perfect an adequate technic of paravertebral alcohol injection. He reported excellent results in 55 per cent of 76 cases and fair results in 21 per cent. Death followed the injection in 8 per cent.[117] Levy and Moore[128] noted improvement in 31 out of 45 patients after this form of therapy. Certain complications have been responsible for the lack of widespread popularity. Pneumothorax[129] and injection of alcohol into the subarachnoid space, with subsequent myelitis, have been reported.[130-132] Intercostal neuritis may appear in a significant number of cases; however, in time it usually disappears.[117, 128] Denervation may not be complete, owing to inaccurate placement of the needle; White has estimated the incidence of regeneration of nerve fibers to be about 8 per cent.[117]

Stellate-Ganglion Block

Stubbs,[133] in 1950, treated 18 patients with angina pectoris by bilateral injection of the stellate ganglions with buffered ammonium sulfate solution. The operation was performed 31 times, on an average of every three or four months, during the course of a year. Results were considered excellent in 13 cases, with immediate relief of pain and freedom from attacks of effort pain for one to six months. The remaining 5 patients were also improved to some degree. There were no deaths. None of the complications usually seen with paravertebral alcohol injection were noted. He saw no reason for operating on the upper sympathetic chain when simple, repeated stellate-ganglion block will allow the patient the maximum activity consistent with his cardiac status.

Pericoronary Neurectomy

Resection of the nerve fibers about the root of the aorta and the coronary vessels was attempted by Fauteux[134] in 1946 in 5 cases. In 4 of these, the great cardiac vein was ligated as well. There was 1 death, and angina pectoris was relieved in 4 cases.

Improvement of the Blood Supply to the Heart

Production of Extracardiac Collateral Vessels

It has been conclusively demonstrated that the blood supply to the heart can be increased by provoking inflammation on the surface of the heart, and by the grafting of some vascular tissue such as mediastinal fat, parietal muscle, omentum, parietal pericardium and lung to the heart surface.[135-142] Various inflammatory agents have been used on the heart, including powdered beef bone,[135] aleuronat,[140] talc,[142] asbestos[144] and a mixture of gelatin, aleuronat, starch, glycerin, water and lionite.[145] In 1935 Beck[135] applied this type of surgery for the first time in a patient, by grafting pectoral muscle to the heart. The patient survived, and the result was good. In 1943, Feil[146] described 37 patients operated on by Beck in whom various tissues were grafted to the heart. There were 14 postoperative deaths, and of the 23 survivors, Feil classified the results as excellent in 14 and good in 5, with little or no improvement in 4. Thompson,[147] using insufflation of

sterilized talc into the pericardial sac, reported a series of 36 cases; 6 patients died, and 26 experienced improvement. Eight patients were said to be completely relieved of angina. O'Shaughnessy,[148] in his experience with 25 cases of angina pectoris treated by cardio-omentopexy and aleuronat, observed relief of angina in 8. There were 5 postoperative deaths. Mason[149] reported 30 cases in which cardio-omentopexy was combined with the use of asbestos and aleuronat; 11 patients died within a few weeks of operation, 3 were not benefited, and 16 were said to have improved. However, in 6 of the 16 the relief was said to be doubtful.

Arterialization of the Coronary Sinus

Gross,[150] in 1937, demonstrated that ligation of the coronary sinus in dogs resulted in an abundant dilatation of intramyocardial collateral channels. Four years later Beck[151] showed that ligation of the coronary sinus provided some protection against occlusion of the descending ramus of the left coronary artery in dogs. Arterial blood was first brought to the myocardium of dogs in 1943 by means of a glass cannula connecting the coronary sinus with one of the great arteries in the neck.[152] Carrying this work further, Beck[153-157] proved that the heart in dogs could be protected against ligation of a major coronary vessel by the delivery of blood from the aorta into the coronary sinus. This was accomplished by anastomosis of a free vascular segment between the aorta and the coronary sinus. The operation was done in two stages. In the first stage the anastomosis was performed; the second stage, which was carried out three weeks later, consisted of partial ligation of the coronary sinus at its ostium. After numerous such experiences and observations on dogs, the procedure was applied for the first time on a patient in 1948, with survival.[158] Subsequently, 12 other patients were operated on; 8 died, and 4 survived. The criteria for selection of patients were then made more rigid, and operations were done on 28 more patients, 5 of whom died. Of the 23 survivors, 13 had both stages of the operation, and 2 underwent only the first stage. In the remaining 8, the operation was unsuccessful owing to thrombosis of the graft in 6 cases and inability to place the graft in 2.[158] Of 18 patients operated on by Bailey[159] the grafts were found to be patent at the time of second stage of the procedure in only 7. Anginal pain was completely abolished in 6. The mortality was 11 per cent.

Ligation of the Great Coronary Vein

Fauteux[160] has demonstrated that ligation of the great coronary vein allowed animals to survive subsequent ligation of the descending branch of the great coronary artery. The aim of the operation is to increase intracardiac collateral circulation by permanently opening anastomotic channels that already exist in the myocardium. After this procedure, one can demonstrate a rise in coronary venous pressure, an increase in retrograde blood flow and a decrease in the oxygen content of the venous blood.[161] The operation was applied for the first time to a patient in 1939, with complete relief of angina for two years, up to the time of writing.[162] In an analysis of 40 cases, the operative mortality was reported as 20 per cent. In the 26 surviving patients the results were classified as follows: 19 patients were free of symptoms and able to return to work; 5 showed improvement and were able to work, but still had some substernal pressure on severe exertion; and 2 had no relief of angina.[163]

Total Thyroidectomy

This procedure was first proposed and carried out in man in 1933 by Blumgart, Levine and Berlin[164] in an attempt to relieve angina pectoris. In 1937 Parsons and Perks,[165] in a review of the literature, were able to find 133 cases of intractable angina pectoris treated by this method. The operative mortality was 3.75 per cent. Seventy-one patients were said to have had excellent results. Of the remainder, 25.1 per cent were moderately and 3.9 per cent slightly improved, and in 12.5 per cent the operation was considered a failure. Cutler,[166] in 1941, reported a five-year follow-up study of 32 patients who had undergone thyroidectomy. There were 12 survivors after five years; 26 of the 27 patients surviving more than six months were relieved of pain for six months or longer, and 8 of the 12 five-year survivors had considerable benefit from the operation. Regarding the rationale for the procedure Cutler[167] considered that the relief of pain that followed total thyroidectomy was related to altered adrenal secretion rather than lowered metabolic rate. The cardiac mechanism is then rendered less sensitive to this hormone. This method of treatment of angina pectoris is rarely employed today in view of the ability of radioactive iodine to achieve the same end without the prohibitive operative mortality.

Prognosis in Angina Pectoris

Recent reports of long-term observations of patients with angina pectoris have indicated that the life expectancy of those afflicted with this disease may be longer than observers formerly thought.[168-171] White, Bland and Miskall[169] followed 500 patients with angina pectoris for over ten years and noted an average survival time of nine years for all patients in the group. Sigler,[171] in an analysis of 1700 cases of angina pectoris and coronary-artery disease, observed that 33 per cent of each sex were alive at the end of five years. In 1946 Parker and his co-workers[170] reported observations on 3440 patients with angina pectoris seen at the Mayo Clinic from 1927 to 1936. Six years later Block et al.[98] reported follow-up studies on these patients and on an additional 3442 patients with angina pectoris. The

five-year survival rate for the entire series was 58.4 per cent, as compared to a rate of 80.9 per cent for the normal population; the ten-year survival rate for the entire series was 37.1 per cent, as compared to a rate of 70.4 per cent for the normal population.

An analysis of these reviews clearly indicates that the survival period of patients with angina pectoris is influenced considerably by such factors as congestive failure, cardiomegaly, hypertension, myocardial infarction and associated debilitating disease. In addition, in a great many cases, the symptomatology of the anginal syndrome is not uninterrupted from its inception to the end, but undergoes variable periods of remission.[172] Because of this, one must be cautious in interpreting the results of treatment in patients.

Summary and Conclusions

The management of angina pectoris has undergone important forward strides during the past several years. Despite these great advances, nitroglycerin remains the preparation of choice in the treatment of the acute attack of angina pectoris. Recent investigations indicate that pentaerythritol tetranitrate may be of some value in diminishing the frequency of attacks of chest pain. The efficacy of the xanthines in the treatment of angina pectoris remains controversial more than fifty years after they were first introduced. These drugs seem to be capable of relieving paroxysms of angina pectoris though their actions are variable and unpredictable. Papaverine appears to produce little subjective or objective improvement in the majority of patients with this syndrome. Hormonal therapy likewise is rarely employed today because of the uncertain results obtained. Khellin has been used with encouraging results in some series, though distressing toxic reactions to the drug are not uncommon. Better purification of visammin seems desirable. The thiourea derivatives have been replaced by radioactive iodine in the management of severe angina pectoris, owing to the greater ease in which a hypometabolic state is established with this agent. The development of myxedema is controlled by small amounts of thyroid. The chief use of anticoagulants appears to be in cases that demonstrate impending coronary occlusion. Experience with the use of blocking agents is limited, and the use of these drugs may be associated with unpleasant side reactions. The importance of weight reduction in the obese patient with angina pectoris has gained recent support. Other measures, quite popular at one time, such as the use of vitamins, cytochrome C and irradiation to the spine and adrenal glands, have fallen into disrepute.

The surgical treatment of angina pectoris is considered only when medical management has failed in a patient who is incapacitated by frequent paroxysms of pain. Of the procedures employed for interruption of pain pathways from the heart, paravertebral alcohol injection is the operation of choice in patients with angina pectoris who are considered poor risks for more extensive procedures. Sympathectomy appears to be of special value in patients with angina pectoris and hypertension, and good results may be expected in a maximum of 57 per cent of cases. Posterior rhizotomy, which has relieved pain in 95 per cent of cases, is a formidable procedure requiring laminectomy but permits severance of the nerve fibers at one operation, and the problem of regeneration of nerve fibers is not encountered. Stellate-ganglion block and pericoronary neurectomy are rarely performed today, and experience with these procedures is limited.

It has been established beyond doubt that the blood supply to the heart can be improved by grafting vascular tissues to the heart and by provoking inflammation on the surface of the heart. Although the performance of this type of procedure may prove beneficial in some patients with angina pectoris, the operative mortality remains high. Arterialization of the coronary sinus has been performed on a substantial number of patients to date, but long-term follow-up studies on these cases are meager. The operative procedure appears to be technically difficult, and the operative mortality is significant. Intracardiac collateral circulation may be improved by ligation of the great coronary vein, with complete diminution of effort pain in 49 per cent of cases.

Total thyroidectomy is no longer utilized in the treatment of angina pectoris in view of the ability of radioactive iodine to achieve the same results without the prohibitive mortality rate.

It should be emphasized that angina pectoris may be attended with variable periods of remission and that caution should be exercised in interpreting results of treatment in patients with this syndrome.

References

1. Morgagni, J. B. *De sedibus et causis morborum per anatomen indagatis libri quinque.* 748 pp. Venice: Topographia Remondiniana, 1761.
2. Heberden, W. Some account of disorder of breast. *Tr. Roy. Coll. Physicians, London* 2:59-67, 1772.
3. Parry, C. H. *An Inquiry into the Symptoms and Causes of the Syncope Anginosa Commonly Called Angina Pectoris.* 167 pp. Bath, England: R. Cruttwell, 1799. Pp. 3-5.
4. Herrick, J. B. Clinical features of sudden obstruction of coronary arteries. *J. A. M. A.* 59:2015-2020, 1912.
5. Voegtlin, C., and Macht, D. L. Action of nitrites and drugs of digitalis group on isolated coronary artery. *J. Pharmacol. & Exper. Therap.* 8:77-86, 1913.
6. Meyer, F. Über die Wirkung verschiedener Arzneimittel auf die Coronargefässe des lebenden Tieres. *Arch. f. Physiol., Leipzig,* 1912. Pp. 223-258.
7. Wayne, E. J., and Laplace, L. B. Observations on angina of effort. *Clin. Sc.* 1:103, 1933.
8. Sollman, T. Nitrites, nitroglycerin and other alkyl nitrates. In *A Manual of Pharmacology.* Seventh edition. 1132 pp. Edited by T. Sollman. Philadelphia: Saunders, 1948. Pp. 445-450.
9. Weiss, S., Wilkins, R. W., and Haynes, F. W. Nature of circulatory collapse induced by sodium nitrite. *J. Clin. Investigation* 16:73-84, 1937.
10. Raab, W., and Lepeschkin, E. Anti-adrenergic effects of nitroglycerin on heart. *Circulation* 1:733-740, 1950.
11. Murrell, W. Nitroglycerin as remedy for angina pectoris. *Lancet* 1: 80, 1879.
12. Gold, H., Kwit, N. T., and Otto, H. Xanthines (theobromine and aminophylline) in treatment of cardiac pain. *J. A. M. A.* 108: 2173-2179, 1937.

13. Leech, D. J. Croonian lectures on pharmacological action and therapeutic uses of nitrites and allied compounds. *Lancet* 2: 123-127, 1893.
14. Levy, R. *Diseases of the Coronary Arteries and Cardiac Pain.* 445 pp. New York: Macmillan, 1936.
15. Winsor, T., and Humphreys, P. Influence of pentaerythritol tetranitrate (peritrate) on acute and chronic coronary insufficiency. *Angiology* 3:1-15, 1952.
16. Perlman, A. Study of therapeutic action and toxicity of pentaerythritol tetranitrate. *Angiology* 3:16-19, 1952.
17. Russek, H., Doerner, A., and Zohman, B. Evaluation of vasodilator drugs currently employed in treatment of coronary disease. Presented before the American Heart Association, Atlantic City, New Jersey, April, 1953.
18. Askanazy, S. Klinisches über Diuretin. *Deutsches Arch. f. klin. Med.* 56:209-230, 1896.
19. Fowler, W., Hurevitz, H., and Smith, F. Effect of theophylline ethylenediamine on experimentally induced cardiac infarction in dog. *Arch. Int. Med.* 56:1242-1249, 1935.
20. Laubry, C., Soulié, P., and Laubry, P. Action de la théophylline-éthyléne-diamine sur la circulation coronarienne. *Arch. d. mal. du coeur* 30:265-282, 1937.
21. Stoland, O., et al. Studies on coronary circulation. IV. A. Duration of coronary dilator action of theophylline ethylenediamine. B. Effect of insulin-free pancreatic extract on coronary circulation. *J. Pharmacol. & Exper. Therap.* 61:387-397, 1934.
22. Starr, I. et al. Clinical study of action of 10 commonly used drugs on cardiac output, work and size: on respiration, on metabolic rate, and on electrocardiogram. *J. Clin. Investigation* 16:799-823, 1937.
23. Master, A. M., Jaffe, H. V., and Dack, S. Drug treatment of angina pectoris due to coronary artery disease. *Am. J. M. Sc.* 197:774-782, 1939.
24. Evans, W., and Hoyle, C. Comparative value of drugs used in continuous treatment of angina pectoris. *Quart. J. Med.* 2:311-338, 1933.
25. Riseman, J. E. F., and Brown, M. G. Medicinal treatment of angina pectoris. *Arch. Int. Med.* 60:100-118, 1937.
26. Gilbert, N. C., and Kerr, J. A. Clinical results in treatment of angina pectoris with purine base diuretics. *J. A. M. A.* 92:201-204, 1929.
27. LeRoy, G. V. Effectiveness of xanthine drugs in treatment of angina pectoris: aminophylline. *J. A. M. A.* 116:921-925, 1941.
28. Williams, N. E. et al. Further observations on effects of certain xanthine compounds in cases of coronary insufficiency as indicated by response to induced anoxemia. *Am. Heart J.* 22:252-266, 1941.
29. Boyer, N. H. Aminophylline and related xanthine derivatives; present status of therapeutic claims. *J. A. M. A.* 122:306-309, 1943.
30. Pal, J. Über die Papaverinreaktion der glatten Muskeln, ihre diagnostische und therapeutische Verwertung. *Deutsche med. Wchnschr.* 39:2068, 1913.
31. Essex, H. E., Wegria, R., Herrick, J. F., and Mann, F. C. Effect of certain drugs on coronary blood flow of trained dog. *Am. Heart J.* 19:554-565, 1940.
32. Anrep, G. V., and Stacey, R. S. Comparative effects of various drugs upon coronary circulation. *J. Physiol.* 64:187-192, 1927.
33. Katz, L. N., and Elek, S. R. Clinical use of papaverine in coronary heart disease. *J. A. M. A.* 122:196-198, 1943.
34. Gray, W., Riseman, J. E. F., and Stearns, S. Papaverine in treatment of coronary-artery disease. *New Eng. J. Med.* 233:389-394, 1945.
35. Simon, A. J., et al. Re-evaluation of papaverine in treatment of angina pectoris. *J. Lab. & Clin. Med.* 34:992-997, 1949.
36. Rinzler, S. H. Present status of medical and surgical therapy in angina pectoris. *Mississippi Valley M. J.* 72:2-9, 1950.
37. Scott, R. C., Seiwert, V. J., Fowler, N. O., Jr., and McGuire, J. Studies on use of dioxyline phosphate in treatment of angina pectoris. *Circulation* 6:125-130, 1952.
38. Edwards, E. A., Hamilton, J. B., and Duntley, S. Q. Testosterone propionate as therapeutic agent in patients with organic disease of peripheral vessels: preliminary report. *New Eng. J. Med.* 220:865, 1939.
39. Walker, T. C. Use of testosterone propionate and estrogenic substances in treatment of essential hypertension, angina pectoris, and peripheral vascular disease. *J. Clin. Endocrinol.* 2:560-568, 1942.
40. Hamm, L. Testosterone propionate in treatment of angina pectoris. *J. Clin. Endocrinol.* 2:325-328, 1942.
41. Sigler, L. H., and Tulgan, J. Treatment of angina pectoris by testosterone propionate. *New York State J. Med.* 43:1424-1428, 1943.
42. Strong, C. F., and Wallace, A. W. Treatment of angina pectoris and peripheral vascular disease with sex hormones. *Canad. M. A. J.* 50:30-33, 1944.
43. Waldman, S. Treatment of angina pectoris with testosterone propionate. *J. Clin. Endocrinol.* 5:305-317, 1945.
44. Summers, V. K. Treatment of angina of effort with androgens. *Lancet* 1:519, 1948.
45. Lesser, M. A. Testosterone therapy in 100 cases of angina pectoris. *J. Clin. Endocrinol.* 6:549-557, 1946.
46. Levine, S. A., and Likoff, W. B. Therapeutic value of testosterone propionate in angina pectoris. *New Eng. J. Med.* 229:770-772, 1943.
47. Riseman, J. E. F. Treatment of angina pectoris: summary of ten years' objective study. *New Eng. J. Med.* 229:670-680, 1943.
48. Levine, E. B., and Sellers, A. L. Testosterone in angina pectoris. *Am. J. M. Sc.* 212:7-11, 1946.
49. Fantl, P., and Salem, S. I. Chellol-glucosid. *Biochem. Zeschr.* 226: 166-179, 1930.
50. Kenawy, M. R., and Barsoum, G. S. Ammi visnaga in treatment of anginal syndrome. *Gaz. Faculty Med., Cairo* 13:33, 1945.
51. Barsoum, G. S., Kenawy, M. R., and El-Sheehy, A. Absorption of khellin and its estimation in blood and tissues. *J. Roy. Egyptian M. A.* 30:312-323, 1947.
52. Conn, J. J., Clark, T. E., and Kissane, R. W. Toxicity of khellin. *Arch. Med. de San Lor.* 1:465, 1950.
53. Hultgren, H., Robertson, H. S., and Stevens, L. E. Clinical and experimental study of use of khellin in treatment of angina pectoris. *J. A. M. A.* 148:465-469, 1952.
54. Anrep, G. V., Kenawy, M. R., and Barsoum, G. S. Coronary vasodilator action of khellin. *Am. Heart J.* 37:531-542, 1949.
55. Scott, R. C., et al. Studies on effect of oral and parenteral administration of visammin (khellin) in patients with angina pectoris. *Circulation* 2:80-88, 1951.
56. Armbrust, C. A., Jr., and Levine, S. A. Treatment of angina pectoris with preparation of khellin (Ammi visnaga). *Am. J. M. Sc.* 220: 127-132, 1950.
57. Best, M. M., and Coe, W. Effect of khellin on coronary artery insufficiency as evaluated by electrocardiographic tests. *Circulation* 2:344-350, 1950.
58. Dewar, H. A., and Grimson, T. A. Khellin in treatment of angina of effort. *Brit. Heart J.* 13:54-60, 1950.
59. Osher, H. L., Katz, K. H., and Wagner, D. J. Khellin in treatment of angina pectoris. *New Eng. J. Med.* 244:315-321, 1951.
60. Greiner, T., et al. Method for evaluation of effects of drugs on cardiac pain in patients with angina of effort: study of khellin (visnammin). *Am. J. Med.* 9:143-155, 1950.
61. Strong, J. E., and Vander Veer, J. B. Khellin therapy in angina pectoris. *Am. J. M. Sc.* 224:186-189, 1952.
62. Conn, J., Kissane, R. W., Koons, R. A., and Clark, T. E. Treatment of angina pectoris with khellin. *Ann. Int. Med.* 36:1173-1178, 1952.
63. Kleiber, E. E. Parenteral administration of ammivin (khellin) in treatment of coronary disease. *Ann. Int. Med.* 36:1179-1189, 1952.
64. Scott, R. C., and Seiwert, V. Treatment of angina pectoris with new crystalline khellin. *Ann. Int. Med.* 36:1190-1197, 1952.
65. Nalesfski, L. A., Rudy, W. B., and Gilbert, N. C. Use of crystalline visammin in treatment of angina pectoris. *Circulation* 5:851-857, 1952.
66. Ben-Asher, S. Further observations on treatment of anginal syndrome with thiouracil. *Am. Heart J.* 33:490-499, 1947.
67. Hollander, G., and Mandelbaum, H. Treatment of angina pectoris with propylthiouracil. *Ann. Int. Med.* 28:1150-1156, 1948.
68. Waitzkin, L. Treatment of angina pectoris with propylthiouracil. *Ann. Int. Med.* 36:1107-1125, 1951.
69. DiPalma, J. R., and MaGovern, J. J. Disadvantages of thiouracil treatment of angina pectoris. *Am. Heart J.* 32:494-503, 1946.
70. Blumgart, H. L., and Freedberg, A. S. Heart and thyroid: with particular reference to I^{131} treatment of heart disease. *Circulation* 6:222-237, 1952.
71. Jaffe, H. L. Cited by Blumgart and Freedberg.[70]
72. Wolferth, C. C., Chamberlain, R. H., and Mead, J. J. Radioactive iodine in treatment of angina pectoris. *Pennsylvania M. J.* 54: 352-358, 1951.
73. Hahn, P. F. Abolishment of alimentary lipemia following injection of heparin. *Science* 98:19, 1943.
74. Gofman, J. W., et al. Blood lipids and human atherosclerosis. *Circulation* 2:161-178, 1950.
75. Graham, D. M., et al. Blood lipids and human atherosclerosis. II. Influence of heparin upon lipoprotein metabolism. *Circulation* 4:666-673, 1951.
76. Engelberg, H. Heparin therapy of severe coronary atherosclerosis with observations of its effect on angina pectoris: two-step electrocardiogram and ballistocardiogram. *Am. J. M. Sc.* 224:487-495, 1952.
77. Russek, H. I., Urbach, K., and Doerner, A. Effect of heparin in cases of coronary insufficiency: evaluation by electrocardiographic tests. *J. A. M. A.* 149:1008-1010, 1952.
78. Miller, H., Zinn, W. J., and Griffith, G. Effect of heparin and placebo therapy in coronary artery disease. *Circulation* 6:679, 1952.
79. Binder, M. J., Kalmanson, G. M., Drenick, E. J., and Roscve, L. Clinical evaluation of heparin in treatment of angina pectoris. *J. A. M. A.* 151:967-970, 1953.
80. Gruner, A., Tage, H., and Flemming, R. Heparin treatment of angina pectoris. *Am. J. Med.* 14:433-437, 1953.
81. Rinzler, S., et al. Effect of heparin in effort angina. *Am. J. Med.* 14:438-447, 1953.
82. Thompson, W. Prevention of coronary thrombosis. *M. Clin. North America* 36:991-999, 1952.
83. Smith, K. S., and Papp, C. Prevention of impending cardiac infarction by anticoagulant treatment. *Brit. Heart J.* 13:467-474, 1951.
84. Acheson, G. H., and Moe, G. K. Some effects of tetraethyl ammonium on mammalian heart. *J. Pharmacol. & Exper. Therap.* 84: 189-195, 1945.
85. Pearl, F. Tetraethyl ammonium chloride — its effects on surface temperatures of extremities in peripheral vascular conditions. *Ann. Surg.* 128:1092-1099, 1948.
86. Atkinson, W. Tetraethylammonium chloride in treatment of angina pectoris. *Am. Heart J.* 39:336-352, 1950.
87. French, A. J., and Doch, W. Fatal coronary arteriosclerosis in young soldiers. *J. A. M. A.* 134:1235-1237, 1944.
88. Yater, W., et al. Coronary artery disease in men 18 to 39 years of age: report of 866 cases, 450 with necropsy examinations. *Am. Heart J.* 36:334-372, 1948.

89. Prager, S. Obesity and heart disease. *M. Clin. North America* **35**: 1351-1359, 1951.

90. Gofman, J. W., and Jones, H. B. Obesity, fat metabolism and cardiovascular disease. *Circulation* **5**:514-517, 1952.

91. Mellinkoff, S. M., Machella, T., and Reinhold, J. Effect of fat-free diet in causing low serum cholesterol. *Am. J. M. Sc.* **220**:203-207, 1950.

92. Hildreth, E. A., Mellinkoff, S. M., and Hildreth, D. M. Effect of vegetable fat ingestion on human serum cholesterol concentration. *Circulation* **3**:641-646, 1951.

93. Block, W., Crumpacker, E. L., Dry, T. J., and Gage, R. P. Prognosis of angina pectoris: observations in 6,882 cases. *J. A. M. A.* **150**: 259-264, 1952.

94. Dublin, L., and Marks, H. Mortality among insured overweights in recent years. In *Reports of the National Life Insurance Companies*. 31 pp. New York: Recording and Statistical Corporation, 1952.

95. Vogelsang, A. B., Shute, E. V., and Shute, W. E. Vitamin E in heart disease: preliminary report. *M. Rec.* **140**:21, 1947.

96. Shute, W., Shute, E., and Vogelsang, A. Vitamin E in heart disease. I. Anginal syndrome. *M. Rec.* **160**:91-96, 1947.

97. Levy, H., and Boas, E. P. Vitamin E in heart disease. *Ann. Int. Med.* **28**:1117-1124, 1948.

98. Baer, S., Heine, W. L., and Gelfond, D. B. Use of vitamin E in heart disease. *Am. J. M. Sc.* **215**:542-547, 1948.

99. Makinson, D. H., Olesky, S., and Stone, R. V. Vitamin E in angina pectoris. *Lancet* **1**:102, 1948.

100. Ball, K. P. Vitamin E in angina pectoris. *Lancet* **1**:116, 1948.

101. Baer, S., and Heine, W. Status of vitamin E in treatment of heart disease. *Mod. Concepts Cardiovas. Dis.* **18**:53, 1949.

102. Proger, S., and Dekaneas, D. J. Some effects of injected cytochrome C in myocardial and cerebral anoxia in man. *J. Pediat.* **29**:729-736, 1946.

103. Bakst, H., and Rinzler, S. H. Effect of intravenous cytochrome C on capacity for effort without pain in angina of effort. *Proc. Soc. Exper. Biol. & Med.* **67**:531-533, 1948.

104. Sussman, M. L. Treatment of angina pectoris by paravertebral short wave irradiation. *Am. J. Roentgenol.* **24**:163-168, 1940.

105. Raab, W. Clinical course of 200 cases of angina pectoris treated with roentgen irradiation of adrenals (1937-1947). *Am. J. Roentgenol.* **63**:895-901, 1950.

106. Russek, H. I., et al. Influence of saline, papaverine, nitroglycerin, and ethyl alcohol on electrocardiographic response to standard exercise in coronary disease. *Circulation* **1**:700-705, 1950.

107. Russek, H. L., Naegele, C. F., and Regan, F. D. Alcohol in treatment of angina pectoris. *J. A. M. A.* **143**:355-357, 1950.

108. Leech, C. B. Personal communication.

109. Levine, S. A., and Harvey, W. P. Temporary relief of anginal pain by carotid sinus stimulation. *Tr. A. Am. Physicians* **60**:255-258, 1947.

110. Freedberg, A. S., and Riseman, J. E. F. Observations on carotid sinus reflex and angina pectoris. *Circulation* **7**:58-70, 1953.

111. Russek, H., Regan, F. D., and Naegele, C. One hundred per cent oxygen in treatment of acute myocardial infarction and severe angina pectoris. *J. A. M. A.* **144**:373-375, 1950.

112. François-Franck, C. A. Signification physiologique de la résection du sympathique dans la maladie de Basedow, l'épilepsie, l'idiotie et le glaucome. *Bull. Acad. de méd., Paris* **61**:565-594, 1899.

113. Jonnesco, T. Angine de poitrine guérie par la résection du sympathique cervico-thoracique. *Bull. Acad. de méd., Paris* **84**:93-102, 1920.

114. Cutler, E. C. Present status of treatment of angina pectoris by cervical sympathectomy. *Ann. Clin. Med.* **5**:1004-1013, 1927.

115. Lindgren, L., and Olivecrona, H. Surgical treatment of angina pectoris. *J. Neurosurg.* **4**:19-39, 1947.

116. Ray, B. Surgical treatment of angina pectoris. In *Disorders of the Heart and Circulation*. Edited by L. R. Levy. 944 pp. New York: Thomas Nelson and Sons, 1951.

117. White, J. C., and Bland, E. F. Surgical relief of severe angina pectoris: methods employed and end results in 83 patients. *Medicine* **27**:1-42, 1948.

118. Evans, J., Poppen, J. L., and Tobias, J. B. Relief of angina pectoris by sympathectomy: report of results in 10 patients subjected to high thoracolumbar sympathectomy including anginal pathway. *J. A. M. A.* **144**:1432-1436, 1950.

119. Kinsey, D., Whitelaw, G., and Smithwick, R. Treatment of angina pectoris in hypertensive patients. *Proc. New Eng. Cardiovas. Soc.* **11**:26, 1953.

120. Poppen, J. L., and Lemmon, C. Surgical treatment of essential hypertension. *J. A. M. A.* **134**:1-9, 1947.

121. Danielopolu, D., and Hristide. Recherches sur la sensibilité cardiaque. Possibilité d'améliorer l'angine de poitrine par la résection des racines postérieures ou des nerfs spinaux. *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:69-73, 1923.

122. Davis, L., and Pollock, L. J. Role of autonomic nervous system in production of pain. *J. A. M. A.* **106**:350-353, 1936.

123. Ray, B. S. Management of intractable pain by posterior rhizotomy. *A. Research Nerv. & Ment. Dis., Proc.* **23**:391-407, 1943.

124. Haven, H., and King, R. L. Section of posterior roots for relief of pain in angina pectoris: observations in 5 cases. *Surg., Gynec. & Obst.* **75**:208-219, 1942.

125. Mandl, F. Die Wirkung der paravertebralen Injektion bei "Angina pectoris." *Arch. f. klin. Chir.* **136**:495-518, 1925.

126. Swetlow, G. I. Paravertebral alcohol block in cardiac pain. *Am. Heart J.* **1**:393-412, 1926.

127. White, J. C. Technic of paravertebral alcohol injections: methods and safeguards in its use in treatment of angina pectoris. *Surg., Gynec. & Obst.* **71**:334-343, 1940.

128. Levy, R. L., and Moore, R. L. Paravertebral sympathetic block with alcohol for relief of cardiac pain: report of forty-five cases. *J. A. M. A.* **116**:2563-2568, 1941.

129. Grant, F. C. Relief of pain in angina pectoris by paravertebral sympathetic block with alcohol. In Stroud, W. D. *Diagnosis and Treatment of Cardiovascular Disease*. Vol. 2. 804 pp. Philadelphia: F. A. Davis Co., 1940. Chap. 38. P. 1185.

130. Molitch, M., and Wilson, G. Brown-Séquard paralysis following paravertebral alcohol injection for angina pectoris. *J. A. M. A.* **97**:247, 1931.

131. Olsen, C. W. Injury to spinal cord and spinal nerve roots in course of paravertebral injection. *Bull. Los Angeles Neurol. Soc.* **6**:131-134, 1941.

132. Huschboeck, F., and Gillespie, M. G. Complication of paravertebral injection of alcohol: report of case. *Arch. Neurol. & Psychiat.* **48**: 320, 1942.

133. Stubbs, J. B., and Woolsey, R. D. Angina pectoris: treatment by injection of stellate ganglia with ammonium sulfate. *South. M. J.* **43**:675-678, 1950.

134. Fauteux, M. Surgical treatment of angina pectoris: experiences with ligation of great cardiac vein and pericoronary neurectomy. *Ann. Surg.* **124**:1041-1046, 1946.

135. Beck, C. S. Development of new blood supply to heart by operation. *Ann. Surg.* **102**:801-813, 1935.

136. *Idem*. Further data on establishment of new blood supply to heart by operation. *J. Thoracic Surg.* **5**:604-611, 1936.

137. Beck, C. S., and Tichy, F. L. Production of collateral circulation to heart. I. Experimental study. *Am. Heart J.* **10**:849-873, 1935.

138. Beck, C. S. Coronary sclerosis and angina pectoris: treatment by grafting new blood supply upon myocardium. *Surg., Gynec. & Obst.* **64**:270-272, 1937.

139. O'Shaughnessy, L. Experimental method of providing collateral circulation to heart. *Brit. J. Surg.* **23**:665-670, 1936.

140. O'Shaughnessy, L., Slome, D., and Watson, F. Surgical revascularization of heart: experimental basis. *Lancet* **1**:617-621, 1939.

141. Vineberg, A. M. Development of anastomoses between coronary vessels and transplanted internal mammary artery. *Canad. M. A. J.* **55**:117-119, 1946.

142. Lezius, A. Die anatomischen und funktionellen Grundlagen der künstlichen Blutversorgung des Herzmuskels durch die Lunge bei Coronararterienverschluss. *Arch. f. klin. Chir.* **191**:101-139, 1938.

143. Thompson, S. Development of cardiopericardial adhesions following use of talc. *Proc. Soc. Exper. Biol. & Med.* **40**:260, 1939.

144. Schildt, P., Stanton, E., and Beck, C. Communications between coronary arteries produced by application of inflammatory agents to surface of heart. *Ann. Surg.* **118**:34-45, 1943.

145. Heinbecker, P., and Barton, W. Operation for development of collateral circulation to heart. *J. Thoracic Surg.* **9**:431-438, 1940.

146. Feil, H. Clinical appraisal of Beck operation. *Ann. Surg.* **118**: 807-815, 1943.

147. Thompson, S., and Raisbeck, M. Surgical rehabilitation of coronary cripple. *Ann. Int. Med.* **31**:1010-1018, 1949.

148. Davies, D. T., Mansell, H. E., and O'Shaughnessy, L. Surgical treatment of angina pectoris and allied conditions. *Lancet* **1**:1-10 and 76-82, 1938.

149. Mason, G. Myocardial ischemia and its surgical relief. *Lancet* **1**: 359-367, 1951.

150. Gross, L., Blum, L., and Silverman, G. Experimental attempts to increase blood supply to dog's heart by means of coronary sinus occlusion. *J. Exper. Med.* **65**:91-108, 1937.

151. Beck, C. S., and Mako, A. E. Venous stasis in coronary circulation: experimental study. *Am. Heart J.* **21**:767-779, 1941.

152. Roberts, J. T., Browne, R. S., and Roberts, G. Nourishment of myocardium by way of coronary veins. *Federation Proc.* **2**:90, 1943.

153. Beck, C. S., Stanton, E., Batiuchok, W., and Leiter, E. Revascularization of heart by graft of systemic artery into coronary sinus. *J. A. M. A.* **137**:436-442, 1948.

154. Beck, C. S. Revascularization of heart. *Ann. Surg.* **128**:854-864, 1948.

155. *Idem*. Revascularization of heart. *Surgery* **26**:82-88, 1949.

156. McAllister, F. F., Leighninger, D., and Beck, C. S. Revascularization of heart by vein graft from aorta to coronary sinus. *Ann. Surg.* **133**:153-165, 1951.

157. Hahn, R. S., and Beck, C. S. Revascularization of heart: study of mortality and infarcts following multiple coronary artery ligation. *Circulation* **5**:801-809, 1952.

158. Beck, C. S., Hahn, R. S., Leighninger, D. S., and McAllister, F. F. Operation for coronary artery disease. *J. A. M. A.* **147**:1726-1731, 1951.

159. Bailey, C. P., et al. Arteriolization of coronary sinus. *J. A. M. A.* **151**:441-445, 1953.

160. Fauteux, M. Experimental study of surgical treatment of coronary disease. *Surg., Gynec. & Obst.* **71**:151-155, 1940.

161. Gregg, D. E., and Dewald, D. Immediate effects of occlusion of coronary veins on dynamics of coronary circulation. *Am. J. Physiol.* **124**:444-456, 1938.

162. Fauteux, M., and Palmer, J. Treatment of angina pectoris of atheromatous origin by ligation of great cardiac vein. *Canad. M. A. J.* **45**:293-298, 1941.

163. Ripstein, C. Results of surgical treatment of coronary artery disease. *Canad. M. A. J.* 59:52-54, 1948.

164. Blumgart, H. L., Levine, S. A., and Berlin, D. D. Congestive heart failure and angina pectoris: therapeutic effect of thyroidectomy on patients without clinical or pathological evidence of thyroid toxicity. *Arch. Int. Med.* 51:866-877, 1933.

165. Parsons, W. H., and Parks, W. K. Total thyroidectomy for heart disease. *Ann. Surg.* 106:722-728, 1937.

166. Cutler, E. C., and Hoerr, S. O. Total thyroidectomy for heart disease: 5 year follow-up study. *Ann. Surg.* 113:245-259, 1941.

167. Cutler, E. C., and Schnither, M. T. Total thyroidectomy for angina pectoris. *Ann. Surg.* 100:578-605, 1934.

168. White, P. D., and Bland, E. F. Further report on prognosis of angina pectoris and of coronary thrombosis: study of 500 cases of former condition and of 200 cases of latter. *Am. Heart J.* 7:1-14, 1931.

169. White, P. D., Bland, E. F., and Miskall, E. W. Prognosis of angina pectoris: long term follow-up of 497 cases: including note on 75 additional cases of angina pectoris decubitus. *J. A. M. A.* 123: 801-804, 1943.

170. Parker, R. L., Dry, T. J., Willius, F. A., and Gage, R. P. Life expectancy in angina pectoris. *J. A. M. A.* 131:95-100, 1946.

171. Sigler, L. Prognosis of angina pectoris and coronary occlusion: follow-up of 1,700 cases. *J. A. M. A.* 146:998-1004, 1951.

172. Boas, E. Natural history of coronary artery disease of long duration. *Am. Heart J.* 41:323-331, 1951.

MEDICAL INTELLIGENCE

VOLUNTARY DEATH BY BREATH HOLDING*

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NEW ORLEANS

OF historic and physiologic interest are various reports of voluntary death by breath holding. These accounts are found in writings from the classical period to modern times. Several of these were collected by Haller,[1] the erudite scholar of catholic interests, and are recorded in his well documented *Elementa Physiologiae* of 1759.

In the classical period cases are referred to by Appianus,[2] Galen,[3] Pliny[4] and Valerius Maximus.[5] Galen[3] cites the case of a foreign slave who in a spiteful anger killed himself by holding his breath (*"Servus barbarus qui, cum vehementi ira concitatus mortem sibi decreuisset prostatus humi, respirationeque cohibita . . . postea mortus est"*). Our translation of Valerius Maximus'[5] account follows:

> There are also foreign deaths worth noting down, and in particular such as that of Coma . . . the mightiest leader of the bandits . . . he was brought before Publius Rupilius, the consul, and when he was questioned . . . having taken time to collect himself he covered his head and leaning on his knees he held his breath, and in the very hands of his guards, and in the sight of the high command, he came to rest, having gained the freedom he desired. Let those unfortunate people for whom death is more advantageous than survival torture themselves seeking, by an anxious and uneasy plan, in what way they will depart from life: let them sharpen the sword, mix poisons, seize nooses, look around for enormous altitudes, as if there should be need of great preparation or elaborate planning, that the union of soul and body which holds them together by a weak bond be destroyed. None of these things did Coma do, but within his chest he held his breath and thus found an end for himself.

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Weber[6] alludes to the death of Cato as another instance of death due to breath holding. The original in Appianus[2] discloses, however, that Cato killed himself by falling on his sword and later eviscerating himself, after threatening to die by holding his breath. The notorious intellectual pack-rat, Pliny,[4] refers to a species of heathcocks that when captured by "retaining their breaths die of mere vexation [*moriunter contumacia spiritu revocato*]."

In modern times examples of this phenomenon are found in the writings of Zucchelli[7] (1712), Cheyne[8] (1733), Dumont[9] (1753), Howe[10] (1859) and Morley[11] (1946). In reporting the famous case of the honorable Colonel Townsend, Cheyne[8] makes no mention of breath holding in the description of the Colonel's death. The case is used by Haller[1] to indicate the voluntary suppression of the heart beat and by Weber[6] as an example of breath holding. Cheyne[8] witnessed only the Colonel's dress rehearsal of his death act on the morning of his demise, and was not present later in the evening when death occurred. He writes as follows:

> He compos'd himself on his Back, and lay in a still Posture some time: while *I* held his right Hand, Dr. *Baynard* laid his Hand on his Heart, and Mr. *Skrine* held a clean Looking-glass to his Mouth. I found his *Pulse* sink gradually, till at last I could not feel any, by the most exact and nice Touch. Dr. *Baynard* could not feel the least motion in his *Heart*, nor Mr. *Skrine* the least Soil of Breath on the bright *Mirror* he held to his Mouth; then each of us by *Turns* examined his *Arm*, *Heart* and *Breath*, but could not by the nicest *Scrutiny* discover the least *Symptom* of *Life* in him. We reason'd a long time about this odd *Appearance* as well as we could, and all of us judging it inexplicable and unaccountable, and finding he still continued in that Condition, we began to conclude that he had indeed carried the *Experiment* too far, and at last were satisfied he was actually dead, and were just ready to leave him. This continued about half an Hour . . . As we were going away, we observ'd some Motion about the Body, and upon Examination, found his Pulse and the *Motion* of his *Heart* gradually returning. . .

A perusal of the rest of Cheyne's[8] book suggests that he is an observer in whom the modern reader would be reluctant to place confidence.

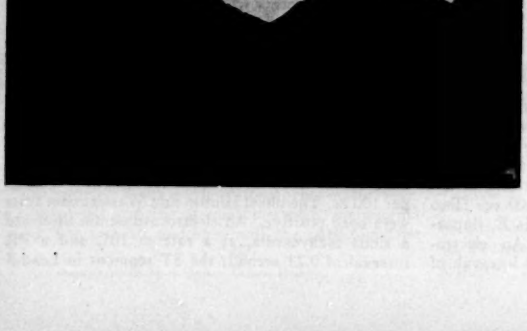
Zucchelli,[7] a Capuchin missionary, recounts his observations on a Negro slave ship in which the morose subjects committed suicide by forcefully inspiring against the glottis, which was obstructed by the base of the tongue. Impressed by the ease with which these persons, free of all infirmity, could accomplish their own demise, he believed them to have pacts with the devil (. . . *e patti, che tenevano col diavolo*).

Dumont,[9] in his history of Louisiana, notes that precautions must be taken during the whipping of Negro slaves lest in anger they suck the tongue into the pharynx and thus die of suffocation. An analogy to the Müller experiment[12] is evident. Dumont's statement regarding this manner of death is: "*Car il est souvent arrivé que dans la rage qui leur cause ce châtiment, il y a eu de ces Negres qui se sont étouffés eux-memes avec leur langue qu'ils renversoient par-dessus le palais, et qu'ils suçoient pour l'avaler.*" A somewhat similar occurrence in Negro slaves is found in the writings of George Howe.[10] A ship's surgeon on a slave ship, he stated that precautions had to be taken to prevent the Negroes from killing themselves in their profound dejection. When a Negro became dejected he would "squat down with his chin in his knees, and arms clasped about his knees, and in a very short time die." The anthropologist, Morley,[11] reports the Mayan Indians "although in good health are able to lie down in their hammocks after announcing their time for death had come and quietly pass away."

Of a similar nature to the above accounts are the episodes of breath holding in children occurring during crying spells.[13] The children, in anger, hold the breath in expiration and quickly become cyanotic. Convulsions ensue if the breath is held beyond thirty to forty-five seconds. Schreiber[14] (1729) believed that death could ensue in normal children. It is held today that the episode is benign except in cases in which underlying cardiovascular disease is present.[15]

References

1. Haller, A. *Elementa Physiologiae Corporis Humani.* Lausanne: 1789. Book 8. Section 13. P. 252.
2. Appianus. *Roman History: The civil wars.* Vol. 3. Book 2. Edited by H. White. New York: Macmillan, 1913. Chap. XIV.
3. Galen, C. De Motu Musculorum. In *Omnia Quae Extant Opera in Latinum Sermonem Conversa.* Fifth edition. Vol. 1. *Primae Classis Libri.* Venetiis apud Iuntas: 1576. Chap. 6. P. 315.
4. Pliny, C. S. *Naturalis Historiae.* Edited by G. Brotier. Vol. 3. Book 10. London: A. J. Valpy, 1826. Chap. 29. P. 1871.
5. Valerius Maximus. *Memorabilia.* Edited by C. Halm. Leipzig: 1865. Book 9. Chap. 12. P. 472.
6. Weber, E. V. Über ein Verfahren, den Kreislauf des Blutes und die Funktion des Herzens willkürlich zu unterbrechen. *Arch. f. Anat. Physiol. u. wissensch. Med.*, 1851. Pp. 88-111.
7. Zucchelli, P. A. *Relazioni del viaggio e missione di Congo Nell' Etiopia inferiore occidentale.* Venezia: Bortolomeo Giavarina, 1712. P. 356.
8. Cheyne, G. Case of Honourable Colonel Townsend. In *The English Malady.* Cornhill and Bath: Strahan & Leake, 1733. Pp. 307-311.
9. Dumont. *Mémoire historique sur la Louisiane contenant ce qui y est arrivé de plus mémorable depuis l'année 1687, jusqu'à présent: avec l'établissement de la colonie Françoise dans cette province de l'Amérique Septentrionale sous la direction de la Compagnie des Indes: le climat, la nature, et les productions de ce pays: l'origine et la religion des sauvages qui l'habitent: leurs mœurs et leurs coutumes, etc. Composés sur les mémoires de M. Dumont de Montigny par M. L. Le Maserier.* Paris: C. J. B. Bauche Librairie, 1753.
10. Howe, G. The Last Slave Ship. In original manuscript (accession number 35015) Oct. 1, 1859 in Louisiana State Museum Library, New Orleans, Louisiana.
11. Morley, S. G. *The Ancient Maya.* 520 pp. Palo Alto: Stanford University Press, 1946. P. 34.
12. Müller, J. *Handbuch der Physiologie des Menschen für Vorlesungen.* Vol. 1. Coblenz: J. Hölscher, 1834-1840. P. 335.
13. Bridge, E. M., Livingston, S., and Tietze, C. Breath-holding spells: their relationship to syncope, convulsions, and other phenomena. *J. Pediat.* 23:539-561, 1943.
14. Schreiber, J. F. *Meditationes Philosophico-Medicae de Lacrumis et Fletu.* 38 pp. Leipzig: Breitkopf, 1729. Chap. 3. P. 28.
15. Dent, J. Personal communication.



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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 39431

PRESENTATION OF CASE

A twenty-seven-year-old female chemist was admitted to the hospital because of fever and headache of one week's duration.

The patient had been born in Poland but had lived in Israel since the age of eight years and had only recently come to the United States. She had had a febrile illness at the age of twelve diagnosed as rheumatic fever. Thereafter she was well until two-and-one-half years before admission, when episodes of acute low-back pain occurred; soon after that an elevated sedimentation rate and persistent low-grade fever were noted. Because of this and the development of a painful red spot on the right great toe she was studied for five months at a hospital in Israel. One blood culture out of twenty grew *Streptococcus viridans* that was very sensitive to penicillin, but she failed to improve on prolonged courses of penicillin and other antibiotics. During this time she had several episodes of fever associated with a skin rash that were treated with ACTH (adrenocorticotrophic hormone). A Kahn test was equivocal. The sedimentation rate remained elevated. In the following year she was studied in the United States, and a presumptive diagnosis of amebiasis was made. However, she did not improve on chloroquin. About sixteen months before admission, after a respiratory infection, she noted stiffness of the fingers and received two six-day courses of cortisone. Since that time she had had persistent brawny pitting edema of the hands. A year before admission she was studied at another hospital, where physical examination was negative except for the edema of the hands. The hemoglobin was 12.5 mg. per 100 cc., and the white-cell count was 5800. Urinalysis was negative. The serum nonprotein nitrogen was 29 mg. per 100 cc. Two blood Hinton tests were positive. An L. E. (lupus-erythematosus) test was negative. An electrocardiogram showed a prolonged PR interval of 0.23 second, as well as slight ST-segment changes that later cleared. Blood cultures were negative. During the year before admission she had noted blanching, coldness and slight pain in the fingers and toes on exposure to cold. The sedimentation rate remained elevated. Five months before admission she began taking butazolidine, 800 mg. daily, and on the tenth day a generalized dermatitis and a high fever developed. Because of this she was given cortisone, 150 mg. daily for three months. Previously, the blood pressure was said to have been normal and urinalyses were negative. On cortisone therapy ankle edema, hirsutism, acne and widening of the face developed. Emotional instability, noted for the three years before admission, became more pronounced upon development of a blood pressure of 190 systolic, 120 diastolic. For two months before admission, she had had severe recurrent headaches, and the swelling of the hands progressed. For the week before entry she had had a persistent tachycardia, a daily fever temperature up to 100.6°F. and nausea and vomiting after almost every meal. On the day of admission she was found to have a pulse of 140 and a +++ test for albumin in the urine. On the afternoon of the day of admission she had the gradual onset over a half hour of severe pain in the anterior portion of the chest radiating to the back.

Physical examination showed a moderately obese woman with "cortisone facies" writhing with pain. Small follicular keratoses were noted in the skin of the bridge of the nose and forearms. The heart was enlarged, the border extending to the left anterior axillary line. There was a Grade 2 apical systolic murmur and an apical diastolic gallop. At the cardiac base the second sound was duplicated. A faint pericardial friction rub was heard over the xiphoid process. The neck veins were full with the patient sitting at 60° and flat at 90°. Fine rales were heard at the left-lung base. The liver edge, which was tender, was palpable 2 or 3 finger-breadths below the right costal margin. There was nonpitting edema of the hands. Ophthalmoscopic examination revealed an albuminuric retinitis, with a few white fluffy perivascular and macular exudates as well as two other white exudates.

The temperature was 98.4°F., the pulse 140, and the respirations 22. The blood pressure was 150 systolic, 134 diastolic.

Urinalysis gave a ++++ test for albumin; the sediment contained an occasional white cell and frequent granular and hyaline casts per high-power field. The hemoglobin was 11.8 gm. per 100 cc., and the white-cell count 21,200, with 86 per cent neutrophils. The nonprotein nitrogen was 42 mg. per 100 cc. The blood Hinton and Wassermann tests were both positive. An electrocardiogram disclosed a sinus tachycardia, at a rate of 105, and a PR interval of 0.23 second; the ST segment in Lead 1

was slightly elevated; the T waves were inverted in Leads 1, 2, V_3, V_4, V_5 and V_6, slightly inverted in Lead V_2, low and upright in Lead 3, flat in Leads aVF and V_1 and diphasic in Lead aVL. Two blood cultures revealed no growth. A catheterized urine specimen demonstrated no organisms on direct smear and no growth on culture. Throat culture grew out abundant nonhemolytic streptococci and moderate alpha-hemolytic streptococci. A roentgenogram of the chest showed the heart to be diffusely enlarged, with a cardiothoracic ratio of 18:25.5 cm. The lung fields were clear, and there was no engorgement of the vessels at the lung roots. Widening of the mediastinal shadow was noted.

On the second hospital day a chest examination revealed diminished breath sounds and dullness over the right lower lobe. The heart sounds were slightly muffled. The patient was started on oxytetracycline, 1 gm. daily. On the fourth hospital day she was noted to be pale, cold and sweaty with heart sounds of poor quality. The temperature rose to 104°F., and she died.

During the last three days of life the temperature ranged between 100 and 104°F.

Differential Diagnosis

Dr. Charles L. Short*: Although it is possible that the febrile illness that the patient had at the age of twelve years constituted the original attack, there is no way of settling this point; therefore, it seems reasonable to date the onset of her illness to two and a half years before entry — that is, about a year before she came to this country. I do not know whether she had a heart murmur or cardiac enlargement when she began to run the persistent fever, but, at any rate, bacterial endocarditis was suspected, and the painful red spot in the great toe perhaps contributed to that suspicion. The diagnosis was not established by consistently positive blood cultures or by a therapeutic test by penicillin. About this time the patient had a severe episode of fever, with a skin rash. It would be interesting to know the nature of this rash, but it seems evident that at this time a generalized connective-tissue disease was suspected since ACTH was employed in therapy. Without further discussion I believe I can assume that she did have such a condition, which, as in this case, often simulates an infectious process in the early stages. I am unable to think of any recognizable infectious process that could produce a clinical picture of the type and duration of her subsequent course. The question is, Which one of these connective-tissue diseases (which is a better term than "collagen diseases" since the pathologic changes are not confined to the collagen fibers)— disseminated lupus erythematosus, rheumatic fever, rheumatoid arthritis, dermatomyositis, scleroderma and polyarteritis nodosa — will the pathologist be able to establish at autopsy? I believe he will be able to make a single diagnosis, although rarely histologic features characteristic of two or more of these connective-tissue diseases occur coincidentally in the same patient. The description of the x-ray findings is reasonably clear in the record. She showed diffuse cardiac enlargement of apparently nonspecific configuration. The lung fields were clear. There was no congestive heart failure as evidenced by engorgement of the vessels at the lung roots, and there was widening of the mediastinal shadow.

First, I might list some of the important points in this patient's history, physical examination and laboratory findings that might be of assistance in diagnosis. She had fever and constitutional symptoms, which are common to all six of the connective-tissue diseases, although much less frequent in the early stages of scleroderma. The vasomotor symptoms that developed in the year before admission are also characteristic of all except rheumatic fever and polyarteritis nodosa. She had a retinitis, which is certainly typical of but not specific for disseminated lupus erythematosus. Such a picture may also be found with dermatomyositis and scleroderma. The small follicular keratoses over the bridge of the nose and on the forearms during the last admission may have been part of the skin manifestations of disseminated lupus erythematosus. I do not think that I could call them diagnostic. There were no mucous-membrane lesions or purpura, both of which are especially common in disseminated lupus. Lymph-node enlargement, at least of the superficial chain, was not noted, but may of course have been found by the pathologist at autopsy. I do not believe its absence is of special diagnostic importance. This patient did have a serositis, with evidence of pericarditis, manifested by a friction rub and by changes in the electrocardiogram. This finding is especially characteristic of disseminated lupus although it may occur in all six connective-tissue diseases. The myocarditis, which was demonstrated by both electrocardiographic changes and cardiac enlargement without obvious valvular disease, may also be found in all of them and is, therefore, not too helpful. Hypertension developed during cortisone treatment, continuing after the cortisone had been omitted about two months before the final admission. Such a finding is more characteristic of disseminated lupus and polyarteritis nodosa but may also occur in advanced stages of scleroderma. If it had been due to polyarteritis nodosa, I should have expected its appearance earlier in the course of the illness. There were no gastrointestinal symptoms or signs beyond nausea and vomiting, which usually appear sooner or later in scleroderma. One manifestation common to all six diseases did not occur in this patient; I refer to arthritis. She had diffuse swelling of the hands,

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which is vaguely suggestive of scleroderma or dermatomyositis, but induration of the fingers with a sclerodermatous feeling has also been described in disseminated lupus. There was no clinical involvement of peripheral nerves, which is a typical finding in polyarteritis nodosa.

Regarding laboratory findings, the urinary changes and the slightly elevated nonprotein nitrogen indicated that she had renal involvement. This, again, is not diagnostic but is most commonly encountered in disseminated lupus and polyarteritis nodosa. The white-cell counts were either normal or, during the final admission, high. This is not especially helpful, but a high white-cell count and polynucleosis by no means rules out disseminated lupus. In one series[1] it was present in about a third of 44 cases at some stage of the disease. It usually occurred in patients with a pyogenic complication or with evidence of spread of the underlying process, especially when they had a high fever or signs of serositis. This patient did not have an eosinophilia.

From the findings I have just enumerated it seems to me that disseminated lupus erythematosus best fits the clinical and laboratory picture although characteristic skin lesions were not present. That the diagnosis can frequently be made in the absence of such signs was shown in a recent series of well established cases from the Presbyterian Hospital,[2] in a third of which skin lesions had not appeared up to the time the paper was written. This has also been our experience here. Two other points fit in well with a diagnosis of disseminated lupus. One is the violent reaction to butazolidine. Drug sensitivity is a common hazard in lupus erythematosus, as we discovered in the early days when sulfonamides were first introduced and were naturally tried in the treatment of this disease. The second is the repeatedly positive serologic tests for syphilis, which I assume were biologically false-positive reactions. Such false-positive tests are found in 20 to 30 per cent of the patients with disseminated lupus erythematosus. In fact it occurs so frequently as to constitute a point of real diagnostic value in any patient with symptoms suggesting a generalized connective-tissue disease or in one who apparently has glomerulonephritis.

I shall conclude with a diagnosis of disseminated lupus erythematosus, which I think the pathologist will be able to establish, although he may also find vascular lesions similar to or even identical with those of polyarteritis nodosa. Polyarteritis nodosa would be my second choice if I had to make one.

One question still to be answered is, What was the exact cause of death? This cannot always be established in disseminated lupus even at autopsy. In this patient no secondary infection, such as the common terminal pneumonia, was evident. She did not die of uremia or any obvious cerebral complication. The terminal events suggested a cardiac complication, tamponade from a pericardial effusion or, as seen in another patient recently, acute arteritis of the coronary system with cardiac infarction. I see no way of establishing either from the evidence available.

I will make a final comment about this patient's treatment. I think it is of more than passing interest that hypertension and obvious renal involvement developed only after the introduction of large doses of cortisone. There is increasing clinical evidence that steroid treatment may favor the development and progression of renal impairment in lupus erythematosus, especially if renal disease is already present. Therefore, great caution should be observed in the use of steroids if there is evidence of kidney damage, and before treatment, renal function should always be adequately evaluated.

DR. CHARLES H. DUTOIT: Our clinical impression was essentially the same as Dr. Short's. I might elaborate briefly on a few points in the protocol that may not be perfectly clear. The febrile reaction with skin rash reported from the original hospitalization in Israel was said to have been associated with the penicillin therapy, and we assumed that the rash was of the nature of urticaria. I gather on rather inadequate evidence that the rash was not suggestive of lupus. For a few months before admission the heart was thought to be normal in size. There was at best a Grade 1 systolic murmur. Over the period of two or three weeks before the final admission there had been a very real change. White-cell counts had been done repeatedly during the two months before the final admission. These were all between 4000 and 5000; in fact a white-cell count done on the morning of admission in another hospital was about 4000. The death was quite unexpected. When the patient was seen at 8 p.m. she had a good pulse pressure, and the venous pressure was no higher than it had previously been. We had been concerned about the possibility of cardiac tamponade all along since on x-ray and clinical examinations it was thought that some fluid was present. However, there had been no change in the pulse pressure on the last day — in fact, it had been somewhat wider than previously. The temperature suddenly shot to 104°F. and she died half an hour later. The temperature in the hospital had been somewhat erratic all along. The last point is that the L.E.-cell preparation was not satisfactory for technical reasons. On the second one several people believed that there was a strong suspicion that L.E. cells were present.

DR. SHORT: Could you describe the hands?

DR. DUTOIT: I think that point was overemphasized. When I first saw the patient she was taking large doses of cortisone and had all the features commonly associated with that therapy. There, was a suggestion that the hands were diffusely swollen, particularly in the proximal phalanges,

without any definite pitting edema. The connective tissue seemed to be somewhat thicker than one would have expected. Pain in the hands — not localized to the joints — had been a prominent symptom in this patient.

Clinical Diagnosis

Disseminated lupus erythematosus.

Dr. Charles L. Short's Diagnosis

Disseminated lupus erythematosus.

Anatomical Diagnoses

Disseminated lupus erythematosus.
Fibrin thrombi, arterioles and capillaries, multiple organs.
Subacute bacterial endocarditis, mitral valve.
Hydropericardium.
Pulmonary edema.

Pathological Discussion

Dr. David Kahn: Autopsy revealed, as Dr. Short predicted, disseminated lupus erythematosus. The pericardial cavity was distended, containing 400 cc. of clear fluid; because we had no way of knowing how rapidly this fluid accumulated we could not determine whether this caused cardiac tamponade. The heart was slightly enlarged, weighing 430 gm. On the atrial surface of the posterior leaflet of the mitral valve along the line of closure was a yellow granular vegetation, 1 by 0.7 by 0.7 cm. The remainder of this leaflet and the other valves appeared normal.

Dr. Short: Did this resemble rheumatic endocarditis?

Dr. Kahn: No; there was nothing to suggest past rheumatic heart disease, and the vegetation was single and larger than those usually seen in the acute stage of rheumatic fever. Microscopically, the valve at the base of the vegetation was scarred and vascularized. The vegetation was composed of dense hyaline connective tissue covered by a layer of fibrin. Gram stain of direct smears revealed numerous gram-positive cocci, in the superficial layer. A few small atypical verrucous endocardial lesions were found in the microscopical sections of the other valves. The large vegetation represented a bacterial endocarditis probably superimposed on an atypical verrucous endocarditis of the Libman–Sacks type. Although grossly the epicardium appeared uninvolved, microscopically there was diffuse focal involvement of this along with similar involvement of the interstitial fibrous tissue of the myocardium; foci of collagen fibers showed the eosinophilic staining characteristically classified as fibrinoid necrosis, and these were associated with some edema and occasionally with a mild inflammatory-cell infiltration. The spleen was enlarged, weighing 570 gm., and microscopically showed well developed periarterial fibrosis of the type rarely seen except in disseminated lupus. Microscopical examination of the kidneys demonstrated moderate involvement, the involved glomeruli revealing the various types of lesions that can be found in this disease: "wire-loop" changes, proliferative glomerulitis, and diffuse involvement of the glomerular capillaries with thickening and distortion.

An unusual microscopical finding was the presence of thrombi occluding the terminal arterioles and capillaries in almost all the organs examined; they were found in the heart, lungs, pancreas, kidneys, spleen, lymph nodes and thyroid and parathyroid glands. There is no question that the predominant disease was disseminated lupus erythematosus. Of interest is the significance of the multiple thrombi found and their relation to the underlying pathologic process. Our first thought was that this was an example of the coincidental occurrence of lupus and the entity, disseminated platelet thromboses. Evidence to suggest a relation between these two conditions has from time to time been presented[3]; the majority of these thrombi stained as fibrin with the differential fibrin stains, and there was no suggestion of endothelial hyperplasia or vessel-wall change, so this possibility was eliminated. Because none of the thrombi suggested embolic fragments and since they were remarkably uniform in size, it seems unlikely that they represented multiple emboli from the endocardial lesions. Other possibilities are that they represented thrombosis secondary to circulatory collapse, with vasodilatation and subsequent slowing of the blood stream, or that they were an expression of a diffuse vasculitis on an immunologic basis similar to that postulated in lupus erythematosus.

References

1. Michael, S. T., and Brown, W. T. Hematologic aspects of disseminated (systemic) lupus erythematosus. *Blood* 6:1059-1072, 1951.
2. Jessar, R. A., Lamont-Havers, R. W., and Ragan, C. Natural history of lupus erythematosus disseminatus. *Ann. Int. Med.* 38:717, 1953.
3. Beigelman, P. M. Variants of platelet thrombosis syndrome and their relationship to disseminated lupus. *Arch. Path.* 51:213-223, 1951.

CASE 39432

Presentation of Case

First admission. A sixty-three-year-old manufacturer was admitted to the hospital because of increasing anorexia and weight loss.

During the five or six months before admission the patient had noted general malaise, increasing fatigue, occasional vague epigastric distress and some constipation, which he related to his poor food intake. He was therefore studied at another hospital two months before admission, where gastrointestinal series and sigmoidoscopy were negative,

but liver studies were positive and he was referred here.

Six years before admission the patient had an acute febrile illness diagnosed as subacute bacterial endocarditis for which he received adequate penicillin therapy for ten or eleven weeks at another hospital. Four years later, cough with nightly hemoptyses began; subsequent studies and roentgenograms of the chest were said to have been positive for tuberculosis. The patient refused hospitalization and continued to work. Later roentgenograms of the chest were said to show improvement. In the two years before admission he was known to have severe hypertension, and recently the blood pressure was 230 systolic, 110 diastolic. There had been mild exertional dyspnea recently and nocturnal dyspnea associated with cough. In the last six months, ankle edema was noted. He had had a high alcoholic intake for many years.

On physical examination there was evidence of recent weight loss. Palmar erythema was noted. The optic disks showed blurring of the margins bilaterally. The arteries were moderately narrowed, and there was arteriovenous nicking. The neck veins were moderately distended but did not pulsate. There was moderate gynecomastia. There were rales over both lung bases posteriorly. The heart could not be outlined. The rhythm was regular, and the aortic and pulmonic second sounds were loud; the aortic second sound was greater than the pulmonic. A Grade 2 to 3 systolic murmur was heard over the entire precordium and was transmitted to the neck. The liver edge was firm, nontender and palpable 5 fingerbreadths below the costal margin. The spleen was firm, slightly tender and palpable 4 fingerbreadths below the costal margin. There was no ascites.

The temperature was 98°F., the pulse 88, and the respirations 16. The blood pressure was 210 systolic, 110 diastolic.

The urine had a specific gravity of 1.022, and gave a + test for albumin; the sediment contained occasional white cells and rare hyaline casts per high-power field. Examination of the blood showed a hemoglobin of 14.2 gm. per 100 cc. and a white-cell count of 10,800, with 87 per cent neutrophils, 11 per cent lymphocytes and 2 per cent basophils; the sedimentation rate was 42 mm. in sixty minutes. The serum protein was 6.6 gm., the albumin 3.6 gm., and the globulin 3.0 gm. per 100 cc. The prothrombin time was 19 seconds (normal, 14 seconds). The cephalin flocculation was ++ in twenty-four and +++ in forty-eight hours. A Congo-red test demonstrated 78 per cent retention in the serum; bromsulfalein retention equaled 16 per cent. A stool guaiac test was negative. Sputum smears were negative for acid-fast bacilli. Roentgenograms of the chest disclosed changes consistent with old tuberculosis at the right apex and a greatly enlarged heart. A barium-swallow examination did not demonstrate any varices.

The patient was discharged on a 3000-calorie, low-sodium diet, brewers' yeast and digitoxin.

Final admission (three months later). The patient returned because of progressive pain in the right side of the abdomen during the previous ten days. He had had weakness, fatigue, anorexia and some fever, but no chills. The stools were light, and the urine dark. No hemoptysis or orthopnea was noted. Since discharge, he had adhered to his diet but had taken digitoxin sporadically.

On physical examination, there was no icterus. The cardiac findings were as before except that now there was a gallop rhythm. Rales were heard over the left lateral part of the chest. The liver edge was felt 5 fingerbreadths below the costal margin and was diffusely tender. The spleen was not felt; there was shifting dullness but no fluid wave in the abdomen. There was ++ ankle edema.

The temperature was 98.6°F., the pulse 102, and the respirations 20. The blood pressure was 196 systolic, 100 diastolic.

Findings on urinalysis were essentially as at the time of the previous admission; there was no bile. The blood hemoglobin was 9.7 gm. per 100 cc., and the white-cell count 12,800, with 93 per cent neutrophils, 6 per cent lymphocytes and 1 per cent monocytes. The serum sodium was 135 milliequiv., the chloride 93 milliequiv., and the potassium 4.4 milliequiv. per liter; the nonprotein nitrogen was 35 mg., the total protein 5.8 gm., the albumin 2.9 gm., the globulin 2.9 gm., the alkaline phosphatase 12.7 units, and the serum bilirubin 1.8 mg. per 100 cc. The stool guaiac test was negative. An electrocardiogram revealed ST-segment and T-wave changes consistent with digitalis effect, hypertrophy of the left ventricle or coronary-artery disease. A roentgenogram of the chest did not disclose any new findings. On a plain film of the abdomen the liver and spleen were enlarged; no opaque calculi were seen.

On the third hospital day, the patient's condition was about the same. There was diffuse tenderness over the liver; the temperature curve was flat at 98.6°F., and the pulse at about 90. However, the white-cell count had risen to 18,400, with 90 per cent neutrophils. The blood hemoglobin was 11.0 gm. per 100 cc.; he had not received any transfusions. During the following night he was uncomfortable and had more pain in the right side of the abdomen and back. On the next morning pain was still present, and he appeared very ill. A surgical consultant confirmed the presence of an enlarged, tender liver and believed that there was more tenderness over the gall-bladder area than elsewhere in the abdomen. He could not feel the gall bladder but believed there was a suggestion of an ill defined mass in that region. Four hours later the patient

was a little more comfortable. The white-cell count was still about 18,000. Later on this day the temperature began to rise and was 100°F. the next morning; the pulse rate was 100. At this time he was moaning and groaning although his appearance was about the same as the day before. There had been no change in the size of the liver. Opinions differed about whether any localization of tenderness had occurred. The temperature and pulse continued to rise. The white-cell count was 20,000.

Later the same day an operation was performed.

Differential Diagnosis

Dr. Claude E. Welch*: In view of this long history, the main problem is to decide whether or not all this abdominal symptomatology can be based on a single diagnosis. I shall have to blame the early story on one diagnosis and assume that something happened on the third day of the second admission that finally precipitated the operation.

I shall proceed from the start of the protocol and see what evidence I can find. The patient was admitted first because of anorexia, weakness and weight loss — symptoms that are far from specific. It is of interest that he was admitted the second time for almost the same reason.

Dr. Daniel S. Ellis: Dr. Angley saw this patient on the outside; is it not correct that you sent him into the hospital because of continued, increasing abdominal pain?

Dr. John C. Angley: He was so tender that he could not tie his bathrobe around his abdomen.

Dr. Welch: In the past he was studied at another hospital. Am I correct in assuming that a barium-enema examination was done, as well as an upper gastrointestinal series?

Dr. Angley: Yes.

Dr. Welch: Six years before admission he had a subacute bacterial endocarditis and apparently had done well. The evidence also points to pulmonary tuberculosis that had been arrested. In addition there was hypertension with evidence of cardiac failure, which was prominent throughout the remainder of the story. The high alcoholic intake, of course, attracts my attention at once because I am concerned here chiefly with the right upper quadrant. On physical examination there was evidence of weight loss, palmar erythema presumably typical of cirrhosis of the liver, vascular disease in the optic fields, gynecomastia (which is in favor of cirrhosis), a few rales and changes in the cardiovascular system indicative of the hypertensive heart disease.

The laboratory tests are of some interest. The white-cell count, though normal, was associated with a marked neutrophilia, and the sedimentation rate was abnormal — out of proportion to the neutrophilia. There was also evidence of liver disease — a low serum protein, an elevated prothrombin time and an abnormal cephalin flocculation test; obviously these chemical determinations, however, did not indicate severe liver failure. Since all sources of hepatomegaly were being investigated, Congo-red and bromsulfalein tests were done; both were slightly abnormal. There was no evidence of bleeding into the bowel.

Apparently at the time of the first discharge, the patient was considered to have cirrhosis of the liver, probably of the portal type, and arteriosclerotic and hypertensive heart disease, and was discharged with the usual measures for those conditions. However, he appeared again three months later because of progressive pain in the right side of the abdomen that, as Dr. Angley pointed out, was severe. Although it was noted here that the stools were light and the urine dark, suggesting common-duct obstruction, the evidence given later indicates that that was not correct.

Physical examination showed no jaundice at this time; the spleen was not felt, but I assume that it was still enlarged because enlargement was later found on x-ray examination; there was a question about the amount of ascites that had now appeared. The laboratory findings had also changed significantly in the three months before the second admission. The facts that there was no bile in the urine and that the serum bilirubin was not elevated are of a good deal of interest. The hemoglobin had declined sharply, and the white-cell count had risen slightly. The blood chemical determinations were not too remarkable except for the low serum protein and the definitely high alkaline phosphatase.

Perhaps we had better see the x-ray films now.

Dr. John F. Gibbons: There are scars in the right apex seen in the lateral view posteriorly that are consistent with tuberculosis of long standing. The lungs are otherwise clear. The heart is enlarged primarily in the region of the left ventricle; the aorta is tortuous but not particularly widened or sclerotic although its border is quite clearly seen so there must be some calcification in it. The films of the abdomen show a large liver; although its lateral border is not visible, the spleen is definitely enlarged. The only other mass in the right upper quadrant besides the shadow that I assume to be the enlarged liver is an ovoid density, which I assume is the kidney. The large and small bowels contain a moderate amount of gas, but there is nothing to suggest intestinal obstruction. There are no calculi.

Dr. Welch: There is not a great deal of evidence of ascites.

Dr. Gibbons: I cannot say that there is any.

Dr. Welch: By the third hospital day the patient had not changed, but then the diffuse tenderness that had been present over the liver became more marked, and he began to complain of severe pain

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in the right side of the abdomen and back. I am a little mystified at this change in the hemoglobin but doubt very much if it was significant. I doubt if he could have become dehydrated that rapidly. The surgical consultant found a marked tenderness over the right upper quadrant and liver and here for the first time raised the question of an acutely infected gall bladder.

There are quite a number of diagnoses to consider for this particular patient. First, this may have been due to some difficulty with the cardiovascular system; in other words he could have had a failing heart as the source of the large, tender liver, and then finally have succumbed to a vascular accident such as a dissecting aneurysm or mesenteric thrombosis. That, of course, must be considered as a possibility. With mesenteric thrombosis it would be a little unusual to have the signs localized quite so sharply to the right upper quadrant as they apparently were. Although other bizarre vascular conditions might be considered, they are unusual enough not to be as likely to be the cause of the trouble as some other conditions.

In the second place, could this have been due to a cirrhosis per se, with some of the terminal findings that occur with a cirrhotic liver? There is good evidence that this man did have cirrhosis that was well compensated since it had not yet caused any severe manifestations. Cirrhosis did not kill this particular patient or lead to his operation. If it was cirrhosis per se, what happened after the cirrhosis developed? He could, of course, have had a hepatoma in the cirrhotic liver, which would give a picture perfectly compatible with this patient's. He could also have advanced to a portal-vein thrombosis, which would lead to a mesenteric-vein thrombosis, but that is not quite typical of what was seen here.

Finally, there is the possibility of straight sepsis. Could he have had a liver abscess? The liver was tender and large all along. If he had a liver abscess, the most likely source would have been septicemia several years before with the subacute bacterial endocarditis; it seems unlikely that he could have harbored a liver abscess this long that finally progressed to the point that it did. Could he have had a simple, ordinary, acutely infected gall bladder hiding under this large liver that could not be localized accurately and that produced these particular symptoms? It is a matter of opinion only, but it seems to me as I go over this story, that there was a progression of a single illness. The severe pain that led to the last hospital admission was progressive; it was not the acute onset that usually occurs with an acute cholecystitis, which I doubt very much was found. I think it is much more likely that the symptoms can all be explained by carcinoma involving the liver, of which hepatoma is the most likely. I say hepatoma because there was no obvious source of any other carcinoma, the x-ray films having been negative, and there was an underlying portal cirrhosis, which is a background for hepatoma. This could account for the pain over the liver, because metastatic or primary carcinoma produces stretching of the capsule. It also could account for the persistently high sedimentation rate that was out of proportion to the neutrophilia. Hepatoma is not inconsistent with the remainder of the findings, which seem to have been those of a chronic progressive wasting disease. I think, therefore, that exploration was performed with the preoperative diagnosis of cirrhosis and a question of an acute cholecystitis, but I think that what was found was cirrhosis, with a superimposed hepatoma.

DR. ELLIS: This patient presented a very difficult problem of deciding whether or not he should be operated on. There was also the question of localization of pain. I believed that the liver was diffusely tender all along its palpable edge; Dr. Robert R. Linton thought that there was definite localization of tenderness and, before operation, that the patient had an acute cholecystitis. On the first admission — incidentally, Dr. Angley suspected that the gall bladder was the cause of the pain before he sent him in — I thought he probably had a large congested liver; his heart was not functioning well, and he had a rapid pulse, gallop rhythm and slightly distended neck veins. However, twenty hours after admission, he was better. When he grew worse on the third day, I thought that he had had a vascular accident of some kind, such as a portal-vein thrombosis with infarction of the liver. His white-cell count steadily rose, with a high neutrophil count, and although I had been opposed to operating on him, he was obviously getting worse and since we did not know what the problem was, our only chance to help him was to operate.

CLINICAL DIAGNOSES

?Cholecystitis, acute.
Cirrhosis of liver, with ? portal-vein thrombosis and infarction of liver.

DR. CLAUDE E. WELCH'S DIAGNOSES

Cirrhosis of liver, portal.
Hepatoma.

ANATOMICAL DIAGNOSES

Intrahepatic hemorrhage and subcapsular hematoma, with rupture into peritoneal cavity.
Cirrhosis of liver, portal.

PATHOLOGICAL DISCUSSION

DR. DAVID KAHN: Since Dr. Linton, who operated on this patient, is not here, would you discuss the operative findings, Dr. Ellis?

DR. ELLIS: At operation we were confronted first of all with a blue-looking peritoneum, which when

opened contained about 500 cc. of gross blood; Dr. Linton removed large clots of blood, perhaps another 500 cc. of clots. The source of the bleeding was found only after great difficulty. The liver surface was definitely that of a moderately severe portal cirrhosis. The gall bladder did not appear to be inflamed; it did have a stone in it. A large, orange-sized mass was present on the undersurface of the liver that through the serosal surface of the liver looked white. When I first saw the mass I thought that it was a hepatoma and that that was the answer to the problem. When the clot around the mass was excavated it was apparent that there had been bleeding posteriorly at the edge of this white surface of the liver. When that white surface was incised, there was a large hematoma in the liver bed beneath the capsule. To my consternation Dr. Linton proceeded to evacuate this, which he accomplished with no further bleeding. The liver surface beneath the hematoma was very granular and looked to me like tumor so biopsies were taken from that area. There was nothing wrong with the bowel and no other evidence of disease.

Dr. Kahn: The specimen from the hemorrhagic area demonstrated an area of subcapsular hemorrhage surrounded by a narrow rim of necrotic liver cells; the microscopical examination actually added no clue to the etiology of this. The biopsy from the nonhemorrhagic granular area of the liver showed the liver lobules separated by bands of fibrous tissue. The gall bladder, which was also removed, showed a low-grade inflammatory reaction in its wall.

Dr. Ellis, will you tell us what happened to the patient after the operation?

Dr. Ellis: After finding this gross bleeding, I still believed that the patient had a neoplasm in the liver that we had not discovered because I could not explain so much bleeding in any other way. Postoperatively he was better for three days and then began to have copious diarrhea and evidence of high intestinal obstruction in that his stomach filled with fluid, which he vomited or which was aspirated in amounts of about 1800 cc. a day. His condition steadily deteriorated. In spite of the problem of maintaining normal fluid and electrolyte balance in the face of obstruction of some kind proximal to the ligament of Treitz and the severe diarrhea, the blood chemical levels remained nearly normal. About the eighth postoperative day he began to have queer attacks in which he suddenly became cyanotic and blue as a grape all over, broke out in cold sweat, felt cold and clammy and had a pulse rate so high that we could not count it. Incidentally, the temperature also began to mount. These attacks occurred for about three days. I was much concerned, but Dr. Edward F. Bland, who saw him, thought that he was having attacks of paroxysmal tachycardia, without evidence of heart failure, and that we had no choice but to carry on. On the night of the tenth postoperative day the patient suddenly complained of severe abdominal pain, his belly became rigid, and he again went into shock. After that the temperature went up to 104 to 106°F. It was obvious the next morning that he had a peritonitis. We believed something else had taken place in the abdomen, the exact nature of which was not known. If he had not been so ill, I think he would have been reexplored, but he was practically moribund then and died twenty-four hours later.

Clinical Diagnoses

Mesenteric thrombosis.
Generalized peritonitis.

Anatomical Diagnoses (post mortem)

Hepatic arteriosclerosis, with infarction, multiple, small, recent.
Healing arteritis, branches of celiac axis.
Generalized arteriosclerosis, severe, celiac, mesenteric, coronary, renal and cerebral.
Infarction of jejunum with perforation and peritonitis, recent.
Coronary thrombosis, with acute myocardial infarction.
Healed ulcerative endocarditis, tricuspid valve.
Cardiac cirrhosis of liver.

Pathological Discussion

Dr. Kahn: At autopsy in the peritoneal cavity we found a loculated cyst in the right upper quadrant below the liver; this contained clear fluid, and there was no evidence of postoperative bleeding from the liver. The remainder of the peritoneal cavity contained 1000 cc. of foul, fecal-stained material, and in the midportion of the jejunum there was a small perforation. A short segment of the jejunum surrounding the perforation was infarcted and necrotic. The liver weighed 2300 gm., and on the undersurface there was a large defect filled with Gelfoam, representing the cavity that had been found at operation. Scattered throughout both lobes of the liver were numerous pale-yellowish, discrete foci in the centers of some of which were areas of reddish discoloration. Microscopical examination showed these to be areas of ischemic infarction, with hemorrhage into some of them; the lesion encountered at operation was one of these, having reached the capsular surface and resulting in bleeding into the peritoneal cavity. The main hepatic artery demonstrated a marked degree of sclerosis, as did its main branches, the lumens of some segments being reduced to a pinpoint size. A number of the secondary and tertiary branches at the hilus showed aneurysmal dilatation with destruction of the elastic tissue and replacement of the muscle coat by vascular fibrous tissue, consistent with a healing arteritis. One

small artery in the head of the pancreas and one in the serosa of the stomach showed a similar change. There was severe generalized arteriosclerosis and arteriolarsclerosis. We assume that the jejunal infarction was on a vascular basis although only severe arteriosclerosis, without total occlusion, was found in the arteries supplying this segment. The liver in some areas not involved by the infarctions was not completely normal. There was a mild fibrosis, which appeared to have a somewhat distinct localization. In scattered areas narrow bands of fibrous tissue divided the liver into irregular lobules; between these areas wide zones of normal liver were present. These fibrous bands appeared to have a relation to the venous system of the liver, and many of the larger veins were dilated and showed phlebosclerosis. The picture suggested a stage in the development of cardiac fibrosis of the liver,[1] and a lesion in the heart was found to account for this.

The heart was of the hypertensive type, weighing 650 gm. and with a left ventricle 2.5 cm. in thickness. There was a healed ulcerative lesion of the tricuspid valve involving all three cusps, which were thickened and distorted. There was a defect of the free margin and line of closure of one cusp, 1 by 1 cm., and evidence of previous rupture of many of the chordae tendineae, which were now represented by short, thickened nubbins of tissue on the undersurface of the cusps. There was no interadherence, but it is impossible to see how this lesion could have failed to cause a substantial amount of regurgitation, although this was apparently well compensated clinically. There was also an acute coronary thrombosis, with myocardial infarction of five or six days' duration, an old cerebral infarct, bilateral fibrocaseous tuberculosis at the apexes and severe nephrosclerosis.

The question is how to classify and explain the lesions in the liver. Was this a separate entity or was it related in any way to any of the other basic pathologic processes — namely, the healed endocarditis, the hypertensive heart disease or the severe generalized arteriosclerosis? The deformed tricuspid valve was mechanically imperfect, and the cardiac cirrhosis indicated some degree of right-sided heart failure. It has been found that sclerosis of the hepatic artery is more severe in cases in which there is an obstruction to blood flow through the liver[2] and in patients with systemic hypertension.[3] Both these conditions were present in this patient. A number of cases[4] of infarction of the bowel secondary to severe mesenteric arteriosclerosis have been reported. We suggest that this was an analogous situation, the hepatic artery and liver being involved. Moreover, we suggest that the medial fibrous replacement may have been due to a previous necrotizing arteritis and was not a separate disease entity but in some way related to the hypertension, arteriosclerosis and obstruction to portal blood flow. Evidence has been presented[5] that necrotizing lesions can occur secondary to raised intravascular pressure, and cases of lesions of this type limited to the pulmonary tree, usually in association with pulmonary hypertension, are not rare.[6] No similar lesions were found outside the area of celiac-artery supply. The small-bowel infarction was presumably the result of severe mesenteric arteriosclerosis alone.

DR. ELLIS: Do you think the bleeding came from a necrotic arteriosclerotic vessel?

DR. KAHN: No, the bleeding was from the area of subcapsular hemorrhagic infarction of the liver tissue itself. We did not find an artery in that area.

DR. WELCH: We have seen it before in the spleen, but I do not recall it in the liver.

DR. KAHN: We have seen cases of generalized polyarteritis nodosa with infarctions in the liver secondary to the necrotizing arteritis, but in none of these to my knowledge did bleeding into the peritoneal cavity occur. I suppose the position of the infarct is governed somewhat by chance, and it would have to be in a certain location for this to occur.

REFERENCES

1. Moschcowitz, E. Morphology and pathogenesis of cardiac fibrosis of liver. *Am. Int. Med.* 36:933-955, 1952.
2. Blumenthal, H. T., Lansing, A. I., and Gray, S. H. Interrelation of elastic tissue and calcium in genesis of arteriosclerosis. *Am. J. Path.* 26:989-1009, 1950.
3. Moritz, A. R., and Oldt, M. R. Arteriolar sclerosis in hypertensive and nonhypertensive individuals. *Am. J. Path.* 13:679-728, 1937.
4. Berman, L. G., and Russo, F. R. Abdominal angina. *New Eng. J. Med.* 242:611-613, 1950.
5. Smith, C. C., and Zeek, P. M. Studies on periarteritis nodosa. II. Role of various factors in etiology of periarteritis nodosa in experimental animals. *Am. J. Path.* 23:147-157, 1947.
6. Hicks, J. D. Acute arterial necrosis in lungs. *J. Path. & Bact.* 65: 535-543, 1953.

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FALL MEETING OF THE COUNCIL

THE fall meeting of the Council of the Massachusetts Medical Society, held in the Boston Medical Library on October 7, 1953, represented, in a way, the official opening of the hundred and seventy-third year of the Society.

So harmonious have been the affairs of the Society during the summer months that the agenda for the meeting was relatively short and no protracted discussions were evoked.

The Subcommittee of the Executive Committee on Blue Cross–Blue Shield Problems had considered six resolutions submitted by the Middlesex South District Society. The first, calling for the establishment of a fee schedule for major medical cases, had been recommended for no action by the subcommittee, and this recommendation had been approved by the Executive Committee. The second, asking for a committee of three physicians from each hospital to review requests for individual consideration of special cases by Blue Shield, was likewise not approved by either the subcommittee or the Executive Committee.

Resolution 3, that Plan B subscribers should be subject to the same restrictions as Plan A subscribers so far as hospital accommodations and private nurses are concerned, was recommended for further study. Regarding the fourth resolution, the first part, that Blue Shield abolish the present $75 limit for major surgical procedures, which had been recommended by the subcommittee, was disapproved by the Executive Committee; the second recommendation, that an assistant be permitted to send a reasonable bill to the patient, was approved.

In regard to the fifth resolution, the recommendation of the subcommittee that no change be made in the present policy of payment for consultation was approved. At present consultations are not paid for by Blue Shield because such liability is so great and subject to so many abuses. The sixth resolution, that Blue Shield designate in the serial number which plan the subscriber holds, was approved in principle and further study was recommended. The Council accepted all the recommendations of the Executive Committee on this report.

After consideration of the report of the Committee on National Legislation, the Council voted to approve the action of the American Medical Association in supporting the controversial Bricker resolution. This resolution, it will be recalled, would limit by a Constitutional amendment the treaty-making powers of the executive branch of the government. The American Medical Association's opposition to extension of old age and survivors' insurance to include physicians in private practice and its attitude toward limitation of medical care and hospital benefits for veterans were also upheld.

A resolution was unanimously adopted congratulating the Worcester District Medical Society on its prompt and thoughtful actions in connection with the Worcester tornado.

The interim organization and appointment of a new committee on employment of cardiac and other

handicapped patients and the appointment of a joint committee with the Massachusetts Nurses Association and the Massachusetts Hospital Association "for the improvement of patient care" were approved.

The President and Secretary of the Society are to be congratulated on their expert conduct of the meeting, which came to a close practically at the moment of serving the Cotting luncheon.

GERIATRICS AND THE LONG-TERM PATIENT

GRANTS totaling $35,000 were recently made through the Commission on Chronic Illness[1] to provide for a second national conference on care of the long-term patient to be held in Chicago, March 18-20, 1954. The American Hospital Association, American Medical Association, American Public Welfare Association and United States Public Health Service are serving as sponsors and supplying the staff, as they did at the first conference three years earlier.

It is hardly necessary to point out that despite the long-term disabilities of wars and accidents it is the illnesses and infirmities of persons in the geriatric age group that comprise the core of the problem to be dealt with at Chicago. Likewise, the multidisciplinary nature of the problem and its threefold challenge in teaching, community service and research merely need to be mentioned. With syphilis reduced by antibiotics in theory, at least, to the status of an acute controllable infection and with tuberculosis primarily a challenge in case finding, early diagnosis and isolation of the sick, the burden of chronic illness today is noncommunicable — in illnesses like cancer, ulcer, hypertensive and cardiovascular diseases, arthritis and diabetes, the etiology of which is poorly understood.

Causation of disease is always multiple; hence no insuperable obstacle to control exists if each factor in the causative complex is not fully understood. For example, many of the dental difficulties of the aged are usually based on caries, a disease complex of many years' duration. Control of caries demonstrates how prevention (by fluoridation) may be initiated before etiology is really understood. Dental caries also illustrates how one of the diseases that become more disabling with advancing years may begin as far back as childhood. In the absence of knowledge of chemical and physical agents, much information about causes useful in control and prevention may be obtained from study of aging persons themselves and of their environment; a problem such as home accidents[2] offers opportunity for analysis of the contribution of infirm persons as well as the obstacles they cope with. Present-day programs undertaken against diabetes and cancer illustrate the application of control rather than prevention at a time when causation is being given more and more emphasis.

Preventive medical teaching and research must not lose sight of the fact that age is not a measure of disease but of time at which the cumulative impact of many diseases is being measured, and that all persons are survivors of a large cohort born on their particular birthdays. Appreciation has been gained that the stage is set for many if not most geriatric conditions such as diabetes, neoplasms, arteriosclerosis and hypertension long before they take their measurable toll in structural changes and death. The stage is set in one of the first six of the seven ages of man. Some of the ailments of the old certainly have their beginnings in childhood — the deafness, for example, that frequently followed chronic otitis media before the advent of antibiotics. Moreover, senescence is a matter of individual tissues and functions as well as years; the milk teeth are dead and shed in childhood; the prizefighter is retired in his thirties and women enter a zone of reproductive geriatrics before they are fifty. Such considerations of selective tissue aging may well have larger implications than are apparent today. A forty-eight-year-old woman giving birth to a child at the menopause stands close to a 5 per cent chance of producing a mongoloid infant destined to enter his own cohort with his nervous system prematurely aged and blighted almost from conception, and certainly from birth. Geriatrics does not stand apart from its multidisciplinary aspects — a fact that must be stressed as much in teaching as in research and practice.

Much is spoken these days of an "epidemiology of health" as well as disease, and at no stage since infancy is the concept of health more amenable to quantitation and definition than in the geriatric age group. Few functions are normal at eighty if normalcy is judged by standards set earlier in life. At advanced age, health is almost as tangible as disease because so many functions are ordinarily depressed and so many structures tinged with disease. Presbyopia, for example, is almost as satisfactory a standard for aging as counting birthdays. A functional goal for aging persons is to be able to contribute something — however little, but as much as possible — to society; the mere avoidance of death like the mere avoidance of disease is neither a medical nor a public-health objective. The contribution must be specified to be measured. Measurement of any function — and hence the effect of age on that function — is meaningless without a frame of reference, just as genetic inheritance is a wholly indefinite concept unless the character or trait selected for study is specified. Aging is to be approached in respect to tissues or functions that age and ultimately die. So viewed aging is seen to have started before birth, with certain embryonic structures like the right aortic arch and the anal membrane; they have their moments of structural and functional existence and then they are gone. One by one the functions of men and women are brought to a halt until people become long-term patients — of concern to themselves and others of a species whose very successes at thinking, procreation and control of disease bid fair to create as many problems as they solve.

References

1. *Chronic Illness News Letter.* Vol. 4. No. 6. August, 1953.
2. Roberts, H. L., and Gordon, J. E. Home accidents in Massachusetts: study in epidemiology of trauma. *New Eng. J. Med.* 241:435-441, 1949.

SPREAD OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI

There have been many reports from Great Britain, Australia and various parts of the United States indicating that the number of strains of staphylococci that are being isolated in large general hospitals and found to be highly resistant to penicillin has been increasing steadily since that antibiotic has come into wide use. This matter has aroused considerable interest and has previously been commented on in these columns.[1, 2] Recently, as chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) gained wide acceptance and usage, the same trend has been revealed in the resistance of staphylococci to these agents. In the most recent study reported from the Boston City Hospital,[3] 73 per cent of the strains of pathogenic staphylococci isolated from all sources were found to be highly resistant to penicillin, 24 per cent to chlortetracycline, and 32 per cent to oxytetracycline. At the time when these three antibiotics first came into use, almost all the staphylococci tested had been moderately or highly sensitive to the agents; only a few were moderately resistant, and none to a degree comparable to that exhibited by some of the strains currently being isolated.[4]

The origin and mode of spread of these antibiotic-resistant strains has received some study. It is readily understandable that during the course of treatment sensitive strains tend to be eliminated, whereas resistant ones may survive and eventually multiply in the patient. The resistant strains may then be transmitted, in turn, to other patients, either directly or by first establishing themselves in the nose and throat of attendants and other personnel of the hospital and then spreading from them to other patients.

There is some indirect evidence that this increase in incidence of penicillin-resistant staphylococci is already being reflected in the community at large. Thus, at the Boston City Hospital, a high degree of penicillin-resistance was found in 55 per cent of staphylococcal strains, initially isolated at the time of admission to the hospital from patients who had never themselves received any penicillin. Of the strains obtained from patients who were undergoing treatment with penicillin at the time, or who had received such treatment recently, 80 per cent or more were resistant. A similar proportion of penicillin-resistant strains was found among staphylococci cultured from patients who had been under treatment for some time with antibiotics other than penicillin, presumably having been acquired from other patients or from the hospital staff.

Resistance to chlortetracycline was found in 7 per cent of strains isolated at the time of admission to the hospital from patients who had never previously received any antibiotics. Strains of staphylococci isolated from patients who were under treatment with either chlortetracycline or oxytetracycline included a much higher proportion of strains resistant to these antibiotics — about 50 per cent to the former and between 60 and 70 per cent to the latter.

It seems reasonable to assume that the hospital is the major focus for the development and dissemination of antibiotic-resistant bacteria. This may be explained by the fact that the greatest proportion of antibiotics are used in hospitals and particularly under conditions that are likely to bring about the emergence of resistant strains — namely, when the antibiotics are given in large doses and for long periods. Dowling, Lepper and others,[5, 6] at the University of Illinois, recently reported an epidemiologic study designed to determine how hospital residence (and the type of antibiotic treatment that it entails) might affect the occurrence of antibiotic-resistant staphylococci in the community. They isolated and studied strains of staphylococci from the nose or throat, or both, when patients were being discharged from a large contagious hospital in Chicago; they then continued to make similar isolations of staphylococci from the same patients at periodic intervals for several weeks after they had gone home. At the same times, they made similar cultures and isolated staphylococci from the household contacts of the patients. Throughout the period of this study they also made repeated cultures of the nose and throat of hospital personnel. All the staphylococcal strains thus isolated were then tested for sensitivity to penicillin and chlortetracycline and were also identified by specific bacteriophage typing.

These studies revealed, first of all, that a high proportion of the staphylococci isolated from the nose and throat of the members of the hospital personnel were antibiotic-resistant; 85 per cent of these strains were resistant to more than 1 unit of penicillin and 64 per cent were resistant to 10 microgm. of chlortetracycline. Of the staphylococci isolated from patients at the time of discharge from the hospital, 88 per cent were similarly resistant to penicillin and 78 per cent were resistant to chlortetracycline. Among the household contacts, between 30 and 40 per cent were resistant to penicillin and about 10 per cent were resistant to chlortetracycline when the cultures were first made — that is, when the discharged patients first joined them at home. Thereafter, the proportion of penicillin-resistant and chlortetracycline-resistant staphylococci among those isolated from the patients decreased steadily until after a few weeks; at that time they reached the same percentage of resistant strains as that found among the household contacts. Among the contacts the proportion of strains resistant to either penicillin or chlortetracycline, or both, did not fluctuate significantly. In the convalescent patients, the proportion of strains resistant to chlortetracycline decreased at a somewhat slower rate than that of the penicillin-resistant strains. Tests for sensitivity of these strains to oxytetracycline and chloramphenicol indicated that the proportion of staphylococci resistant to each of these agents paralleled that of the chlortetracycline-resistant strains. The identification of the strains in the patients and in the household contacts by means of phage typing revealed a continuous transfer of strains from patients to household contacts, and vice versa, throughout this period.

The Chicago workers postulated that antibiotic-resistant staphylococci may appear in the nose and throat by three different mechanisms: by treatment with antibiotics, by transfer of resistant strains within the hospital, or by transfer within the community. On the basis of the results presented, all three modes of transfer were regarded as important. It also seems likely, however, that a similar increase in resistance of strains may occur among members of households of patients who are receiving treatment with antibiotics in the home, particularly when the treatment is given for long periods and with large doses, although the over-all effect must be much less striking. It also seems likely that this phenomenon is not limited to the staphylococcus, though it is perhaps more strikingly demonstrated with this organism than with other organisms. The discovery of a way to halt, reduce

or even reverse this trend of increasing antibiotic resistance in pathogenic bacteria offers a real challenge to investigators in this field.

References

1. Editorial. Penicillin-resistant staphylococci. *New Eng. J. Med.* 242: 382-384, 1950.
2. Editorial. Pathogenicity of penicillin-resistant staphylococci. *New Eng. J. Med.* 244:888, 1951.
3. Finland, M., and Haight, T. H. Antibiotic resistance of pathogenic staphylococci: study of five hundred strains isolated at Boston City Hospital from October, 1951, to February, 1952. *Arch. Int. Med.* 91:143-158, 1953.
4. Finland, M., Frank, P. F., and Wilcox, C. *In vitro* susceptibility of pathogenic staphylococci to seven antibiotics (penicillin, Streptomycin, Bacitracin, Polymyxin, Aerosporin, Aureomycin, Chloromycetin): with note on changing resistance of staphylococci to penicillin. *Am. J. Clin. Path.* 20:325-334, 1950.
5. Dowling, H. F., Lepper, M. H., and Jackson, G. G. Observations on epidemiological spread of antibiotic-resistant staphylococci, with measurements of changes in sensitivity to penicillin and aureomycin. *Am. J. Pub. Health* 43:860-868, 1953.
6. Lepper, M. H., Dowling, H. F., Jackson, G. G., and Hirsch, M. M. Epidemiology of penicillin- and aureomycin-resistant staphylococci in hospital population. *Arch. Int. Med.* 92:40-50, 1953.

1954 PRIZE-ESSAY COMPETITION

THE *Journal* again announces the prize-essay competition open each year to fourth-year medical students in schools approved by the Council on Medical Education and Hospitals of the American Medical Association. The response in the 1953 contest justifies the expectation that many members of the class of 1954 will submit papers of high quality.

As in previous years, the essay will consist of the report of a clinical case personally studied by the student. As before, the report will be combined with a discussion of the pathologic condition represented by the case and a review of the important literature on the subject, the paper following the usual form of case reports as published in the *Journal*. Thus the participant not only will lay himself, or herself, open to the possibility of winning a substantial prize but will do so in the ordinary course of academic duty.

The other rules of the competition are as follows:

Manuscripts are to be not more than 5000 words in length, clearly typewritten in English, double or triple spaced with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be in the hands of the editor by March 15, 1954, and must be accompanied by a certification from the dean of the medical school concerned stating that the author is a member in good standing of the fourth-year class and specifying the expected date of graduation. All manuscripts will become the property of the *Journal*.

A cash prize of $100 will be paid for the best essay of those found to be suitable for consideration; the paper will be published in the *Journal* if the quality is considered to conform to the standards by which the editors usually judge material submitted, and the author will receive a hundred free reprints.

A second prize will consist of a two-year subscription to the *Journal*.

The editors wish to emphasize that in establishing this competition they are interested as much in encouraging good medical writing as in promoting the collection of scientific and clinical material. In judging papers that may be submitted, particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

From various sources, accounts of the disgraceful quarrels among the physicians of Cincinnati reach the East, some of which have already been given in the Journal.

Boston M. & S. J., *October 26, 1853*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The November schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

Orthopedic Clinic	Date	Clinic Consultant
Salem	November 2	Paul W. Hugenberger, M.D.
Gardner	November 3	Carter R. Rowe, M.D.
Haverhill	November 4	William T. Green, M.D.
Greenfield	November 5	Charles L. Sturdevant, M.D.
Lynn*	November 9	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	November 12	George W. Van Gorder, M.D.
Lowell	November 13	Albert H. Brewster, M.D.
Springfield	November 18	James D. Fisher, M.D.
Pittsfield	November 18	Edward J. Coughlin, Jr., M.D.
Hyannis	November 19	Paul L. Norton, M.D.
Worcester	November 20	John W. O'Meara, M.D.
Fall River	November 23	David S. Grice, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	November 3, 10, 17, 24
Fitchburg	November 4, 11, 18, 25

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Clinic in the Lynn Hospital.

CORRESPONDENCE

TRIBUTE TO JAMES F. BALLARD

To the Editor: On October 19 Mr. James F. Ballard celebrated his seventy-fifth birthday among his many friends, collaborators and admirers. He was born in 1878, and has been associated with the Boston Medical Library since 1892, first as an errand boy and then as an assistant librarian, and since 1927 as director of this institution.

Mr. Ballard has distinguished himself as an administrator, librarian, bibliographer and author of contributions dealing with

his specialty. He has helped the growth of the library. As a brilliant administrator he has introduced many innovations in the daily routine of the library: he has also acquired many valuable and rare books for reduced prices and rendered great service to many medical research workers. He is the author of two books and many book reviews and various notes on medical subjects. He improved the system of cataloging books in libraries, thereby facilitating the use of books. His principal accomplishments consist in the simplification of medical-book classification and his work on incunabula and sixteenth-century medical books and as review editor of the *New England Journal of Medicine*.

Mr. Ballard is congratulated on the occasion of his seventy-fifth birthday. We register his excellent work and productivity in his chosen field. We wish him many years to come in good health and creative work.

SOLOMON R. KAGAN, M.D.

Roxbury, Massachusetts

NOTICES

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Massachusetts General Hospital and the Boston City Hospital on Monday, November 2, at 8 p.m., at Morse Auditorium, Museum of Science, Boston.

PROGRAM

Massachusetts General Hospital. Edward F. Bland, M.D., presiding:

Cardiac Tamponade: Clinical Experiences and Relief by Pericardial "Window." Drs. C. Williams and L. Soutter.
Borderline Findings in Rheumatic Fever Subjects: With special reference to sounds and murmurs. Dr. A. L. Friedlich.
The Use of a Potent Carbonic Anhydrase Inhibitor, "Diamox," in the Treatment of Congestive Heart Failure: A cooperative study. Drs. A. Leaf, W. B. Schwartz (New England Center Hospital) and A. S. Relman (Massachusetts Memorial Hospitals).

Boston City Hospital.

The "Slatting Sail" Sign of Mild Pulmonic Stenosis. Drs. J. W. Dow and M. N. Alimurung.
Effect of Prolonged Heparin Administration of Angina Pectoris and Serum Lipoprotein. Drs. H. L. Chandler and G. V. Mann.
Clinical Observations on 500 Patients Undergoing Mitral Valvuloplasty. Drs. D. E. Harken and L. B. Ellis.

Interested physicians, medical students and members of the New England Postgraduate Assembly are cordially invited to attend. Free parking facilities are available on the premises at Science Park.

SYMPOSIUM ON INDUSTRIAL NURSING

A symposium on industrial nursing, sponsored by the Boston College School of Nursing, The Liberty Mutual Insurance Companies, the American Association of Industrial Nurses and the Massachusetts Industrial Nurses Association, will be held from 9 a.m. through 5 p.m. on three Saturdays, October 31, November 7 and 21, at the Boston College School of Nursing, 126 Newbury Street, Boston. The topics will be presented by specialists and will include industrial nursing practice, handling of injuries and the compensation law, exposures to occupational disease and the role of industrial health in the country's problem of medical care.

ROCKY MOUNTAIN HARVARD MEDICAL SCHOOL ALUMNI ASSOCIATION

The sixth annual Harvard Lecture, under the auspices of the Rocky Mountain Harvard Medical School Alumni Association, will be given by Dr. Elliott P. Joslin at 5 p.m., October 30, in the Sabin auditorium, University of Colorado Medical Center, Denver, Colorado. The subject will be "Diabetes, Today and Tomorrow."

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 25–29. American Institute of Dental Medicine. Page 124, issue of July 16.

OCTOBER 26, NOVEMBER 2 and 9. Fried Lectures. Page 634, issue of October 8.

OCTOBER 27. Hampden District Medical Society. Page 634, issue of October 8.

OCTOBER 27. Kenneth D. Blackfan Memorial Lecture. Page 672, issue of October 15.

OCTOBER 28. New England Obstetrical and Gynecological Society.

OCTOBER 28. Phi Delta Epsilon Graduate Club of Boston. Page 634, issue of October 8.

OCTOBER 28–DECEMBER 2. Course in child psychiatry (pediatric neuropsychiatry). Page 428, issue of September 3.

OCTOBER 30. Rocky Mountain Harvard Medical School Alumni Association. Notice above.

OCTOBER 31, NOVEMBER 7 and 21. Symposium on Industrial Nursing. Notice above.

NOVEMBER 2. New England Cardiovascular Society. Notice above.

NOVEMBER 2–4. New England Postgraduate Assembly. Hotel Statler, Boston. Page iv, issue of October 15.

NOVEMBER 2–25. Consultation Clinics for Crippled Children. Page 713.

NOVEMBER 2–DECEMBER 21. Hartford Medical Society Program. Page 260, issue of August 6.

NOVEMBER 6 and 7. American College of Cardiology. Page 506, issue of September 17.

NOVEMBER 6–DECEMBER 18. Boston Lying-in Hospital Journal Club. Page 672, issue of October 15.

NOVEMBER 12–14. Annual Convention of the National Society for Crippled Children and Adults. Chicago.

NOVEMBER 18. Massachusetts Society of Examining Physicians. Page 546, issue of September 24.

NOVEMBER 19 and 20. Inter-Society Cytology Council. Page 170, issue of July 23.

DECEMBER 6. American Academy of Dental Medicine. Page 170, issue of July 23.

MAY 31–JUNE 3, 1954. American Urological Association. Page xvii, issue of July 23.

SEPTEMBER 12–15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

OCTOBER 27. (Combined with the Auxiliary.) Roger Smith Hotel, Holyoke. 6:00 p.m.

MIDDLESEX EAST

NOVEMBER 18.

JANUARY 20. (Combined with the Auxiliary.)

MARCH 24.

MAY 12. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 29

THURSDAY, OCTOBER 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

12:00 m.–1:00 p.m. New England Center Hospital Conference. I. The Mechanism of Hypotension Oliguria. II. Some Effects of Splanchnicectomy on Renal Function. Dr. Edward Meilman. Stearns Auditorium, New England Center Hospital.

*4:30–5:30 p.m. Hypertension — Physiological Mechanism and Pathological Response and Management. Dr. J. Grybouki. Nurses' Home, Cambridge City Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

*8:15 p.m. Introduction to Electrocardiography (with slides). Dr. David Rutledge. Joslin Auditorium, New England Deaconess Hospital.

(*Notices concluded on page xvii*)